

**The Globalisation of the Pharmaceutical Industry**

**PHARMACEUTICALS POLICY AND LAW**

## Pharmaceuticals Policy and Law

### Volume 18

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# The Globalisation of the Pharmaceutical Industry

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**Volume 18, 2016**

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## Editorial – The innovation and access to landscape

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The biopharmaceutical industry is playing a vital role in both innovation and access to medicine through intensive research and development (R&D), partnerships, patient access programs, and through contributions to good governance.

Firstly, it is a high-technology sector that invents and develops life-saving and life-enhancing medicines, reinvesting more of its net sales back into innovative research than any other industry (14.4% on average) [1].

As evidence of the above, despite the complexity and unpredictability of the innovation process, the industry has developed more than 550 medicines in the last 15 years for some of the world's most critical and emerging health needs, including oncology, cardiovascular disease, and diabetes [2,3]. During the past 5 years, 182 novel drugs to treat major public health concerns have been approved by the US Food and Drug Administration (FDA), with 45 approved in 2015 alone [4]. Industry continues to be instrumental in exploratory research, as well as translating research into patient-ready life-saving and life-enhancing medicines to those in need [5].

The new medicines and vaccines springing from the work of scientists over decades created a legacy from which every one of us benefits today. Effective medicines and vaccines do more than prevent and treat diseases, and patients are not the only ones who are helped by new developments. When new medicines improve a population's health, also the economy benefits from a healthier workforce.

Having the right medicines is just one step in improving public health. A shared goal in the global health community, including the industry, is to ensure the world's patients receive the medicines they need to live longer and healthier lives. Expanding access to health care and to medicines can be complex and challenging, particularly in low- and middle-income countries, and requires a structured, collaborative effort that ensures health systems use resources effectively and efficiently. Ensuring that patients receive the correct medication, at the appropriate time and from a convenient location, requires a complex 'value chain' [6]. There are many gaps in health care systems that have an unequal impact on populations.

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It should be recognized that a holistic approach to access to medicines should be adopted and enforced by the competent international and domestic health authorities. National procurement and supply systems for medicines are often inefficient, or poorly calibrated to meet current needs. As a result, scarce resources are wasted, the introduction of vital new medicines is delayed and stock-outs may occur, presenting a significant barrier to health.

Strong regulatory systems are needed to ensure that people around the world have timely access to quality medicines and vaccines that are both effective and safe. Today, only 20% of the World Health Organization's Member States have well developed pharmaceutical regulatory systems, due to considerable human and financial resources that such systems entail. In a globalized world, however, the regulatory landscape needs to evolve continuously to address old and new challenges. The safe and effective supply of medicines will become an increasingly important global priority in the 21<sup>st</sup> century [7]: providing effective protection against falsified medicines is to be considered a shared goal, in the interests of individuals and communities all over the world.

The most promising solution is to make regulatory systems work more efficiently through convergence and harmonization. For example, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry representatives to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development [8]. Another important and more recent example is offered by the African Medicines Regulatory Harmonization (AMRH) Programme [9]. As stated in the goals of this initiative, in "harmonizing medicines regulations, a positive impact will be made on:

- Access: Communities get quicker, greater access to priority essential medicines of good quality.
- Availability: The availability of affordable essential medicines can be improved through simplified, harmonized, efficient and transparent regulatory approval processes.
- Affordability: With more generics (lower priced) on the market, patients can achieve greater savings. Governments and donors can enjoy cost savings from subsequent downward pressure on prices through enhanced competition and pooled (shared) procurement."

The UN Sustainable Development Goal 3.8 calls upon the world to "achieve universal health coverage, and provide access to safe and effective medicines and vaccines for all" [10]. Every year, the pharmaceutical industry develops new solutions that have potential to transform health outcomes; for many, however, even basic healthcare services are beyond their reach. Weak systems and incoherent policies exacerbate inequalities rather than resolving them, making poverty both a primary determinant and ongoing consequence of poor access to healthcare.



In order to secure continued business investment in innovation, and to ensure access to care and achieve strong health systems around the world, all actors, including industry, need to collaborate, share accountability and target sustainability across all health system components and especially for essential medicines, vaccines, diagnostics and health technologies. The Agenda for the Sustainable Development Goals 2030 calls for a “revitalized global partnership,” including the private sector, particularly to address access to medicines [11].

The constant quest for new mechanisms to improve access to medicines will not be successful unless they are pragmatic and respond to the realities of the complex global health landscape, engaging a coalition of actors in both the public and private sector.

Product development partnerships, innovative financing mechanisms, voluntary licensing and non-assert declarations, have helped the biopharmaceutical industry reach hundreds of millions of people in under-resourced settings already. Few essential medicines are covered by any intellectual property. Where IP does exist, the industry has demonstrated that it is prepared to work on new models and approaches to expand access for patented products. Where IP is not a sufficient incentive to stimulate R&D for diseases of poverty, the industry has an impressive track record of pursuing innovative partnerships and collaborative approaches to share the costs and risks of R&D on which no commercial return can be expected [12].

The viability of the pharmaceutical industry depends on the existence of functional pathways that bring medicines to the people who need them, and industry is committed to engage in strengthening health access as a central part of its global operations.

Together with government, non-profit organizations, and multilateral organizations, industry is addressing healthcare access as a complex, multidimensional issue that requires comprehensive and varied approaches.

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## Introduction – Lessons for developing a sustainable life sciences eco-system in MICs and LICs

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A healthy life sciences eco-system<sup>1</sup> is an environment where all stakeholders, patients, researchers, governments, the civil society and manufacturers, work together to support the sustainable development and provision of innovative solutions that address unmet health needs. To build a stronger eco-system, governments could prioritise policy initiatives such as: facilitating the commercialisation of academic research; encouraging clinical research; accelerating the adoption and diffusion of new innovative medicines; and promoting the local market as a place to invest and deliver life sciences innovation [1].

Historically, the development of medicines has been primarily undertaken in, and for the benefit of, high income countries. Over the last 20 years, this has started to change, partly as a result of the market opportunity increasing in middle-income countries (MICs) and low-income countries (LICs) and partly because governments in these countries have recognised the importance of encouraging innovative industries, resulting in a greater priority given to addressing diseases highly prevalent in MICs and LICs.

In this article, we draw on our experience to develop lessons on how to establish a sustainable life sciences eco-system in MICs and LICs. We highlight the importance of different types of government policy (industrial policy, the regulatory framework, intellectual property, and improving access to medicines) and how success requires different stakeholders (public and private, international and national) to work together.

Keywords: Policy, lessons, life science, eco-system, sustain, Africa, China, India, Brazil, pharmaceuticals, medicines, LICs, MICs

### 1. Encouraging innovative pharmaceutical activity in MICs and LICs

In recent years, there has been increasing interest in encouraging innovative pharmaceutical activities in developing countries [2,3].<sup>2</sup> We define innovation<sup>3</sup> as “a

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<sup>1</sup>The life science ecosystem has been defined as “an environment and infrastructure that supports pioneering researchers and clinicians to bring innovation to market earlier and more easily, making the given market the location of choice for investment”. As defined by the UK Government in its “Strategy for UK Life Sciences.” 2011.

<sup>2</sup>This section is based on prior CRA studies: CRA and International Federation of Pharmaceutical Manufacturer and Associations (IFPMA), Policies that encourage innovation in Middle-Income Countries, October 2012 and CRA, IFPMA and INTERPAT, Policies that encourage pharmaceutical innovation in Africa, pending publication.

<sup>3</sup>We particularly focus on product innovation in original molecules or biologics, product variants, dosage formulations or fixed combinations but also on innovation in the production process.

multi-phased process, beginning with lab-based research and leading to patentable inventions before moving into the different stages of clinical research, which is then translated into safe, effective and commercially viable products from which society gains a benefit in terms of improved health” [2]. Although the majority of R&D spending continues to be concentrated in high income countries, the proportion spent on R&D in developing countries has increased. Indeed, pharmaceutical spending data show an increase of the proportion spent in ex-US and European countries from 6.6 percent of the total in 2009 to 7.5 percent of the total in 2014. From a regional perspective, the absolute level of spending in ex-US and Europe regions is the highest in Latin America, followed by Asia Pacific, with Africa continuing to lag behind. However, estimates of five-year growth from 2009–2014 show that Latin America and Africa have exhibited higher growth than Asia Pacific [4].

To understand the role of different policy levers in encouraging innovation, we examined different MICs (including China, Brazil, India, South Africa, Russia and, most recently, focused on the situation in different African markets, such as Kenya and Nigeria) along the R&D chain from basic research or discovery activities, followed by preclinical research, clinical trials (Phase I-III), registration and post-registration or phase IV trials. The analysis included desk research as well as interviews with local policymakers and academic experts.

While early stage research activities still largely occur in high income countries, there are an increasing number of R&D centres in China and a small number of hubs in development in countries such as India, Brazil, and Russia [5].<sup>4</sup> Moving along the R&D value chain, it is widely recognised that research institutions and corporations are looking to developing markets to undertake clinical studies. However, the ability of MICs in attracting clinical trials depends on the phase of the trial [6]. Phase I and II clinical trials are mostly located in North America and Europe, countries in Asia or Latin America have been successful in attracting Phase III and IV clinical trials.<sup>5</sup> However, there are notable exceptions with a significant number of Phase I trials in China and Russia. A proxy to assess innovative activities in countries is also the number of people employed in R&D. Data on researchers specifically employed by the pharmaceutical industry is scarce, however, we can compare the overall number of researchers per capita. In this case, the regional leaders are China, Russia, Brazil and South Africa. Other countries, such as Malaysia in Asia and Kenya in Sub-Saharan Africa, are making progress [7–9].

Another way to measure progress is the level of output from the innovative process. The number of scientific publications is often used as a proxy for early stage

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<sup>4</sup>CRA analysis based on public information of IFPMA members. Of the 27 members, we collected data on the location of R&D centres for 20 companies as of 20 August 2012.

<sup>5</sup>Data from [clinicaltrials.gov](http://clinicaltrials.gov), a clinical trials registry that includes recruiting, active, completed, and inactive clinical trials. Trials are registered by pharmaceutical firms as well as national institutes. This means that trials not registered will not be shown in the analysis. Additionally, trials which are on multiple phases are counted more than once.

research. In terms of scientific publications, China, South Africa and Brazil all lead in their respective regions [10]. A second widely used measure, is the number of patent applications and those that are subsequently granted. The latter has grown significantly in MICs, with India, Brazil and China displaying an increase of 19 percent, 22 percent and 5 percent respectively. In contrast, markets such as Russia and MICs in Africa, remain less active in this area [11].

Ultimately, innovation should be assessed by the impact on patients and the health-care system. This is difficult to determine because scientific advances take decades to reach patients. In addition, new medicines are often developed through actions taking place in a variety of countries, making it increasingly difficult to attribute the innovative output to a single country. With the exception of a small number of new chemical entities, it is not surprising that the number of medicines developed in MICs remains relatively small and largely represent incremental innovations, such as reformulations or expansion of the use to different patient groups. Indeed, only in China, Nigeria and India<sup>6</sup> do we find some evidence of novel medicines developed in the domestic market.

#### *1.1. Policies that encourage capacity building for innovation activities and incentivise innovation*

In order to derive lessons on policies that encourage innovative activities and incentivise innovation, we have documented government policies used in the case study countries mentioned above and how these have changed over time. Policies affecting innovation are commonly described as encouraging innovation through a 'technology push' or as influencing the social and economic market opportunities that incentivise innovation through a 'market pull' mechanism [12].

Most MICs and LICs have a national plan or national innovation strategy (NIS) to encourage innovative industries, but there are significant differences with respect to overall focus and objectives, and policy instruments advocated. In some countries, the primary focus is on life sciences or the pharmaceutical industry, while in others the innovation strategy spans across many sectors. Even where plans are specific to life sciences, some aim to develop manufacturing, while others focus on R&D. Further, some focus on encouraging innovation through public organisations, while others focus on motivating the private sector.

It is challenging to determine the impact and relative success of these policies in innovation, or how this may depend on the nature of the plan. However, the development of a coherent NIS is often seen as a necessary condition to build a sustainable pharmaceutical industry, as there is some correlation between success in encouraging innovative activity and the maturity of the planning [13]. In the set of countries

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<sup>6</sup>Examples of novel medicines developed in domestic markets are: H1N1 influenza vaccine by Sinovac in China, Melfian Plus for the treatment of malaria by Cipla in India and Nicosan/Niprisan for treatment of sickle-cell disease by NIPRD in Nigeria.

we studied, Brazil and China established NIS in the early 2000s, followed by India and African MICs which set up similar policies from 2010 onwards. The quantitative evidence on the impact of these plans on innovation remains limited [2]. Looking at the different traits of NIS and through discussions with stakeholders in countries, we identify a number of success factors for policy content and implementation. Indeed, evidence suggests that successful plans: are developed through a cooperative process including government, academia and industry; have clear objectives; focus on both public and private sector initiatives; emphasize implementation and understand that the latter needs time. All of these factors positively impact NIS success [2].

Although a national plan is an important signal of a country's intent to develop an innovative industry and a guide for policymaking, success depends on the capacity to undertake different activities along the value chain. Early stage and preclinical research requires the best academic and research capabilities. A world-class institution or research group is seen as essential to developing this capability. In addition to the amount invested in education, the way the funding is spent is also important. Critical investments include the development of specific skills such as biological sciences; achieving academic excellence through both domestic education and attracting labour trained abroad; and building skills through cooperation with industry, for example student internships at life sciences companies.

Even in a more interconnected world, the location of different activities continues to remain important. Companies in clusters are found to be more inventive and sustainable [14]. Most MICs have identified the development of clusters as a policy priority and have facilitated this through improved infrastructure, funding for research in these hubs and other indirect financial incentives. However, developing successful clusters is not straightforward. Evidence from available literature and an analysis of a number of MICs, shows there are more failures than successes [15]. Experience also suggests that clusters are more successful when they: develop organically such as in India;<sup>7</sup> focus on building collaboration between public and private entities; have financial and regulatory incentives for multinational companies to locate their activities there and reflect the type of innovative activity from early stage to clinical research and manufacturing.

Encouraging innovation also depends on funding. For MICs and LICs, government support and public research is often identified as a key policy component and there is evidence that this has encouraged innovative activity. For example, in South Africa, public funds have been dedicated to research activities on diseases that impose a specific burden on the country. In return this has given South Africa a comparative advantage in these disease areas. However, our research suggests that government action alone, focused on public investment, is not sufficient to create a healthy

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<sup>7</sup>India has a diversity of clusters, each with a different focus. Andhra Pradesh has research and manufacturing facilities and is home to the Genome Valley. Bangalore is composed of small biotechnology companies and CROs. Hyderabad only hosts manufacturing facilities. Although some government policies were encouraged, these were mainly developed through market forces.

life sciences eco-system. Public investment should develop the research infrastructure and be a complement to private investment. An even more successful approach encourages private participation along the value chain, as illustrated by policies facilitating technology transfers. Technology transfers help to develop stronger links between local and international industry, government and academia. In Brazil, the government has encouraged technology transfer for many years [16].

A healthy life sciences eco-system also encourages collaboration between industry and academia. Reforms allowing university researchers to work with industry have been important in accelerating the commercialisation of university-developed technologies and encouraging public-private partnerships. Although all stakeholders recognise that collaboration between industry, government and academia is a key element to promote innovation, this requires a change in the relationship between academia and industry and takes time to develop. The experience of stakeholders in MICs is that encouraging collaboration is vital to successful domestic innovation and works best through voluntary agreements.

Direct international support can also be an important determinant of innovation in MICs and LICs. Indeed, there is a positive relationship between foreign direct investment (FDI) and the level of innovative activity. The decision to invest in a market is driven by many factors including the pharmaceutical market size and growth rate, as illustrated by the high levels of greenfield investment by pharmaceutical multinational companies in China, but also by government policy [17]. Policies that encourage a stable, predictable environment are key factors for determining the level of FDI. In addition to the direct impact of FDI as a source of funding for innovative activities, it is useful as it can improve capacity to undertake innovation. Involvement in international clinical trials sponsored by international companies increases the capacity to develop domestic clinical trial programmes [16]. However, the long-term impact of FDI depends on the type of investment. Not all FDI in MICs and LICs has directly translated into the development of innovative activities and often focuses primarily on encouraging manufacturing. It is important that FDI policy targets investment along the innovative value chain.

Encouraging innovative activity requires a robust and predictable regulatory framework. The pattern of clinical trial activity in case study countries reveals that success in attracting clinical trials has been directly linked to the regulatory systems and the speed of response of regulatory agencies.<sup>8</sup> In particular, we find the number of clinical trials depends on market access potential (e.g. China and Russia), patient

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<sup>8</sup>There are many papers examining the characteristics that make countries attractive as a location of clinical trials. As reported by the OECD 2011, Kearney (2006) developed a “country attractiveness index for clinical trials” based on five categories of variables: patient pool (size, availability), cost efficiency (labour, facilities), regulatory conditions (e.g., regulation, intellectual property [IP] protection), relevant expertise (e.g., clinical research organisations [CROs], skilled labour force), and infrastructure and environment (e.g., IP protection, country risk). The overall results put the United States at the top, followed by China, India, Russia and Brazil.

pool (e.g. India has more treatment-naïve patients), clinical infrastructure, availability of low labour costs (e.g. China and India) but also regulation that is consistent with international best practice and allows clinical trials to be initiated efficiently. The implication for developing the regulatory framework differs depending on the type of country. Many MICs have adopted similar approaches to those found in the US or Europe. In addition, for some MICs and LICs, collaboration on regulatory rules and capabilities appears particularly important.

### *1.2. Case example: The Southern Africa Development Community*

In regions where development of regulatory systems is limited, coordination offers the opportunity to share learnings and pool resources to optimise the process. For example, in Africa the regulatory framework for medicines in many parts of the continent remains largely underdeveloped. In 2002, the Southern African Development Community (SADC) was established to undertake a campaign to ‘harmonise’ the pharmacovigilance (PV)<sup>9</sup> systems across all member countries by introducing a ‘minimum standard’ to improve the quality, safety and efficacy of medicines circulating within the region, and to establish and maintain a regional shared network system for regulatory authorities [18]. This has similar traits to the Good Pharmacovigilance Practices (GVP), a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU [19].

Given the current level of PV infrastructure and progress in SADC countries, these are classified into three categories. In order to harmonise the approaches to PV, countries have joined up regardless of their ‘level’ with the aim to share experiences and knowledge [20]. The objective is that all SADC countries will be in the upper level by 2019. This emphasises the tremendous impact collaboration and harmonisation policies have in creating a sustainable life sciences environment in MICs and LICs and the different approaches that can be used to develop the regulatory framework.

Finally an appropriate national IP environment is fundamental to pharmaceutical innovation as it rewards companies for commitment to high R&D spending. Evidence suggests the nature of a country’s IP regime affects the willingness to conduct R&D activities there [21]. Indeed, research across countries has found that in MICs, including Brazil and China, a change in the level of patent protection has led to changes in innovative activities. However, this relationship, and particularly the causality, remains complex and any analysis needs to account for other factors such as the level of education, scientific capabilities and infrastructure, as described above [22]. Drawing from our research, we find that a strong IP regime is necessary, but not sufficient in itself, to promote innovation from both domestic and international companies and affect the location of clinical research. This is one of the reasons that China has been relatively more successful at attracting inward investment in

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<sup>9</sup>In regulatory processes, the use of PV, defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.



research, for example, relative to India, where product patents were only recognised in 2005 and whose IP regime is perceived as weaker by international companies. For domestic innovators more heavily reliant on rewards from their domestic marketplace, the importance of IP is even greater.

### *1.3. Bringing together industrial and health policy*

Finally, to successfully encourage innovation and a sustainable ecosystem there needs to be consistency between industrial policy and health policy. Innovative activity directly focused on the health burden of the country provides an additional motivation for policymakers to encourage the activity further. Policymakers and companies often discuss whether they should focus on innovation for the global market or the domestic market. Case study countries differ considerably in terms of whether they are focusing on global diseases (diabetes, cancer, cardiovascular) or diseases more prevalent in their markets. For example, innovative activity in South Africa primarily focuses on HIV, tuberculosis and hepatitis; Brazil targets some neglected diseases; whilst India and China employ research and innovation efforts on global diseases and opportunities.

The interaction between industrial policy and health policy can be represented in a virtuous circle. At a local level, health policies that support the domestic healthcare infrastructure, through improving clinical standards and ensuring access to modern medicines, improve the clinical research environment by establishing the infrastructure, human expertise and other resources such as patient registries, which improve the ability to conduct high quality clinical studies [23]. In return, encouraging local innovative activity, contributes to overall healthcare goals. For example, local research or clinical trials grants immediate access to medicines to some patients, facilitate value assessment and the pricing and reimbursement process, advocate the value of medicines through improved physician awareness and contribute to the education of the latter [24]. This is consistent with evidence of a positive relationship between the level of spending on healthcare, the level of spending on patented medicines and the amount of clinical activity in countries [25]. Therefore, it is important to establish a coordinated approach to policy, encompassing industrial and health policy strategies, in order to support domestic innovation. However, there remains a concern that policies to encourage innovative activity are inconsistent with improving patient access to medicines. We turn to this in the next section.

## **2. Strengthening access to medicines**

To investigate the relationship between policies to encourage innovative activities and access to medicines, we have considered the case study of HIV/AIDS. HIV/AIDS is a relatively recent disease, first clinically recognised in 1981. It is amongst the top 10 causes of death worldwide, particularly in MICs and LICs [26].

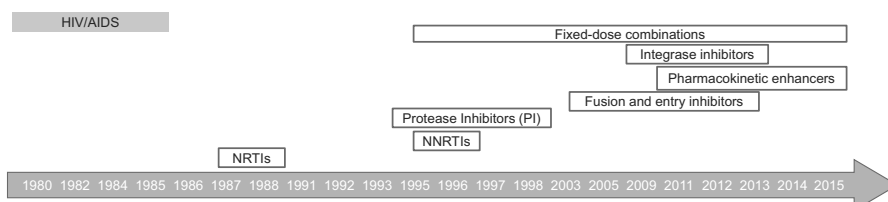


Fig. 1. The evolution of innovation in HIV. Source: CRA analysis.

Over the last 30 years, a plethora of new medicines have been developed (Fig. 1) [27]. The first HIV/AIDS anti-retroviral drug was zidovudine, a nucleoside reverse-transcriptase inhibitor. Soon after there followed a new paradigm of medicines, including protease inhibitors, non-nucleoside reverse – transcriptase inhibitors and combination therapies of these different drug classes.

### 2.1. Access to HIV/AIDS treatments

Over the last 20 years, improving access to HIV/AIDS treatments has been a global policy priority with the creation of The Global Fund, and initiatives such as U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and Clinton Health Access Initiative(CHAI) playing a significant role. At a supra-national level, the World Health Organization (WHO) has created and periodically revised treatment guidance to account for new innovations and has encouraged their uptake. Most recently in 2015, the WHO recommended Antiretroviral therapy (ART)<sup>10</sup> for all adults and adolescents with HIV, regardless of CD4 counts and included six first-line treatment alternatives [28]. Within a few years of the 2010 WHO guideline revisions for treatment of HIV/AIDS, 90% of all countries adopted the new recommendations, illustrating the role that supranational guidance on treatment alternatives can play in encouraging uptake of innovation.

At the national level, MIC and LIC governments have committed (to varying degrees) to tackling the HIV/AIDS epidemic and introduced and implemented national plans. For example, MICs such as Brazil, Botswana and LICs such as Rwanda put in place national plans before 2000 to ensure domestic investment and resources to build healthcare infrastructure, from care centres to healthcare professional training. A statistical analysis on determinants of access finds the date of national plans for HIV/AIDS is correlated to the level of ART access, suggesting that countries like South Africa that denied HIV/AIDS as a legitimate problem for a number of years has been forced to play catch-up throughout the last decade [29]. There is also evidence that, where there is a reduction in the national prioritisation, barriers

<sup>10</sup>The 2015 WHO recommendations have succeeded the 2014 WHO recommendation that ART should be initiated in all individuals with CD4 count < 500 cells/mm<sup>3</sup>.

to accessing medicines may arise. The Indian National AIDS Control Organisation (NACO), created in the early 1990s, devotes 1/6th of its budget to the provision of HIV/AIDS treatment. A budget reduction over the last two years has meant a reduction in staff training for voluntary HIV testing, which ultimately impedes access to ART as HIV/AIDS patients who are not diagnosed cannot be treated [30].

## 2.2. *How the international community has changed the HIV/AIDS trajectory*

The investment in healthcare infrastructure is clearly important, with spending on health and HIV/AIDS specifically positively associated with ART coverage. The substantial increase in resources from the international community, dedicated to promoting health over the last several years, has changed the trajectory of the HIV/AIDS epidemic in the poorest countries. Only after The Global Fund, PEPFAR, the Bill & Melinda Gates Foundation and UNAIDS focused resources did access start to improve for the poorest countries [31–34]. MICs have mostly funded their own programmes although they have also been able to leverage the experience of multi-lateral agencies to their benefit. Again, there appears to be little conflict between prioritising improvement in health funding and efforts to encourage innovative activity. We do not find IP to be an important determinant of access to ART.

Drawing on the case studies, the innovative industry has contributed to the affordability of ARVs through voluntary licensing and differential pricing, which emerged as a common practice at the beginning of the decade. Initiatives such as the Accelerating Access Initiative, a partnership between international organisations and industry, has sought to provide preferential prices to countries in order to improve the affordability of HIV/AIDS treatment. At the same time, generic manufacturers, often using voluntary licence agreements, have played an important role in all of the case studies. For example, this has meant that Sub-Saharan Africa countries like Rwanda and South Africa<sup>11</sup> have been able to supply a large proportion of first line ARTs with generic alternatives. This has been largely facilitated by the Medicines Patent Pool (MPP)<sup>12</sup> and by generic manufacturers. Most recently, a novel product, dolutegravir, was voluntarily licensed through the MPP to the least developed countries, Sub-Saharan African countries and all lower income MICs [35].

## 3. **Implications for developing a sustainable life sciences ecosystem**

There are a number of policy implications for facilitating innovation and access to medicines in MICs and LICs. Although it is often argued that there are tensions

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<sup>11</sup>Between 2004 and 2006, the total percentage of first line ARVs procured = 65% generic, 35% branded. Chien (2007), HIV/AIDS Drugs for Sub-Saharan Africa: How Do Brand and Generic Supply Compare? Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1805689/>.

<sup>12</sup>The MPP is a United Nations backed organisation that partners with the industry to provide generic manufacturing licenses for HIV treatment (also viral hepatitis C and tuberculosis).

between industrial and health policy, we find that they are complementary and should be considered together in a joined up policy approach.

First, a consistent and long term policy commitment is imperative for encouraging innovative activity and improving access to innovative medicines. Our evidence demonstrates that, long-term consistent innovation policies, adapted for different parts of the innovation value chain, are important for the sustainability of the system. This reflects the length of time it takes to develop innovative capacity and the long life cycle of investment to develop new medicines. Upgrading the regulatory framework across developing countries has been a lengthy process which requires collaboration and sharing of best practices. Long term political commitment is equally crucial to facilitate access to medicines. As illustrated in the HIV/AIDS case study, MIC and LIC governments like Brazil, Botswana and Rwanda who established national strategies to address the HIV/AIDS epidemic early on, benefited from a significant change in access to ARVs that remains observable to this day. Maintaining these policies over time through updating and refreshing these programmes is also vital if access is to improve for underserved populations, especially children and people in rural areas, who still lack access to medicines [36–39].

Second, IP protection is a necessary component for developing and rewarding the pharmaceutical industry and fostering the life sciences eco-system. While IP protection is not in itself sufficient to sustain innovation, MICs and LICs that establish and guarantee the protection of IP ensure manufacturers a return on investments in R&D. IP protection recognises that the on-patent and off-patent industry contribute in different ways to improving access to medicines. We do not find a conflict between encouraging innovative activity and improving access to medicines. Indeed, looking at the case of HIV/AIDS, it is clear that the innovative pharmaceutical industry has increased the availability and affordability of ARVs through differential pricing and voluntary licensing agreements. At the same time, the generic industry has also played its part in implementing these IP agreements by producing and distributing medicines to patients.

Third, there needs to be cooperation between the stakeholders within the life sciences eco-system. This ensures a sustainable value chain drawing on the expertise and funding from public, private and academic sectors. The access to medicines is also dependent on coordination between international organisations, civil society, manufacturers and national governments. It is clear that efforts by the WHO, PEPFAR, and The Global Fund in partnership with industry and governments, have facilitated the immense improvement in access to HIV/AIDS treatment over the last 15 years.

Fourth, investment in infrastructure is necessary for innovative activity and to improve access to medicines, which are mutually re-enforcing. For MICs and LICs, improving education and the scientific base are fundamental elements for attracting innovative activity. This includes investment in academia but also in healthcare professionals. As medicines are launched in the market, healthcare infrastructure is key to ensuring patient access. Access to ART for HIV/AIDS works best when integrated

programmes are used to ensure diagnosis, testing and maintenance of patients on a course of treatment. Healthcare centres built to diagnose and distribute ARTs and the infrastructure to facilitate patient access to those centres also helps improve access to medicines for other infectious and non-communicable diseases and encourages innovative activity.

Finally, there is no single approach to encouraging innovative activity or improving access to medicines (the key components of a health innovation eco-system). Lessons from other countries can provide a guide and useful options to consider but industrial, regulatory and health policy should be tailored to each country's circumstances and evolve to reflect changes in the capabilities and needs of society.

### Conflict of interest

The views expressed herein are the views and opinions of the authors and do not reflect or represent the views of Charles River Associates or any of the organizations with which the authors are affiliated.

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## The globalization of medicines as a challenge for governments

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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 TTIP 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 exclusivity 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 inter-governmental 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.

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## Compulsory licensing: Procedural requirements under the TRIPS agreement

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Compulsory licenses of patents under the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) are often mistakenly viewed as a solution to problems relating to access to medicines in developing countries. Access requires a strong political commitment, a health system that contains multi-disciplined health professionals, and an adequate infrastructure to enable transportation of patients and equipment. The use of compulsory licenses should be a rare event considered only under extremely limited circumstances and not an instrument of industrial policy. If a government decides to issue a compulsory license, there are several technical and procedural requirements that must be satisfied under TRIPS. This paper explores those requirements and examines instances where courts have issued decisions relating to compulsory license requests or grants. It analyses the key provisions of TRIPS that are relevant to a government grant of a compulsory license without the authorization of the right holder. It also provides examples and analyses of previous grants of compulsory licenses that have been deficient in meeting on more more procedural requirements under TRIPS.

Keywords: Patent law, compulsory license, World Trade Organization (WTO), Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)

### 1. Introduction

Intellectual property protection mitigates the scientific, regulatory, and economic risks of pharmaceutical innovation because inventors are afforded time to recoup investments in research and development (R&D). In addition, national intellectual property (IP) policies should be flexible enough to anticipate social and economic changes. This balance is reflected in the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which requires WTO Members to provide a minimum level of IP protection, but leaves the precise manner of implementation to each WTO Member. Certain “flexibilities” relating to IP protection and enforcement are incorporated into TRIPS. For example, WTO Members may provide “more extensive protection” than required in TRIPS, as expressly indicated in TRIPS Article 1.1. This provision acknowledges that such protections may be beneficial to developing an enabling environment for innovation in particular markets. A WTO Member can also include certain limited exceptions to rights conferred by TRIPS, such as the limited exceptions to patent rights found in TRIPS Article 30. In addition, Article 31 of TRIPS provides that WTO Members may permit the use of a patented invention without the authorization of the

right-holder, under certain defined circumstances. Such unauthorized use is generally referred to as a “compulsory license.”

Compulsory licenses of patents are sometimes mistakenly viewed as a solution to the problem of access to medicines in developing countries. However, while permissible under TRIPS in certain limited circumstances, compulsory licenses are only intended as an option of last resort in extraordinary circumstances. They are not a sustainable solution to access problems, which are generally not a result of patents or other intellectual property protection [1]. Achieving sustainable access is complex and requires different elements to work together. First and foremost, access requires strong political commitment, a health system that contains multi-disciplined health professionals, and adequate infrastructure to enable transportation of patients and equipment [2]. Routine use of compulsory licenses is not consistent with the intent of TRIPS, provides only short-term solutions that risk undermining long-term needs, and, rather than enhancing access, could instead discourage the introduction of new medicines. Frequent use of compulsory licenses weakens the global intellectual property framework and critically undermines the incentive system that underpins the ability of the private sector to undertake essential R&D, especially capital-intensive and high-risk pharmaceutical R&D. Compulsory licenses are also less effective than other mechanisms and access initiatives [3], as it can take much longer to manufacture and deliver treatments than to secure a voluntary license via direct negotiations with the patent holder, or to utilize tiered pricing initiatives. History has demonstrated that compulsory licenses are seldom used because other mechanisms facilitate medicines procurement in a more efficient and sustainable manner. In appropriate circumstances, voluntary licenses often provide more than a simple license to the patents and may include rights to underlying technologies, know how, and technical expertise. Another mechanism with demonstrated effectiveness is a non-assertion declaration of intellectual property rights. This option is similar to voluntary licensing, but instead of active involvement by an innovator company, an agreement is reached that intellectual property rights will not be asserted, provided that certain criteria, like product quality and geographical distribution, are met. Access to medicines in developing countries is also further enhanced by tiered-pricing policies and numerous product donation programs.

The use of compulsory licenses should be a rare event, considered only under extremely limited circumstances, rather than an instrument of industrial policy. Nonetheless, before a government decides to issue a compulsory license, there are several technical and procedural requirements under the TRIPS Agreement that must first be satisfied. This paper explores those requirements and examines instances where courts have issued decisions relating to compulsory license requests or grants. Section 2 analyzes the key provisions of TRIPS that are relevant to a government grant of a compulsory license without the authorization of the right holder. Section 3 provides examples and analyses of previous grants of compulsory licenses that have been deficient in meeting one or more procedural requirements under TRIPS.

## 2. TRIPS – Key provisions relating to compulsory licenses

The key provision relating to compulsory licenses in TRIPS is Article 31, entitled “Other Use Without Authorization of the Right Holder.” However, this is not the only provision that is relevant for governments wishing to ensure that a compulsory license grant is legally and procedurally compliant with TRIPS. It is first important to look at the general requirements of Article 27, which are imposed on all WTO signatories.

Paragraph 1 of Article 27 TRIPS states:

Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. . . . [P]atents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and *whether products are imported or locally produced*.

The “non-discrimination” clause in Article 27.1 clarifies that a patented invention must be accorded similar rights and protections, regardless whether the manufacturer produces the patented invention locally or chooses to import the invention. Thus, if a government considers whether to authorize use of a patented invention without the consent of the patent holder, it cannot legally use as the basis for that authorization the fact that the patented product in question is imported. The non-discrimination provision of Article 27.1 recognizes that in any modernized industrial sector, it would be highly impractical to suggest that a company could or should build manufacturing plants in every country in which the company wishes to conduct business.

Article 30 of TRIPS further clarifies that WTO members may provide exceptions to the rights of the patent holder, but that such exceptions must meet three criteria: 1) the exception must be limited; 2) the exception must not unreasonably conflict with normal exploitation of the patent; and 3) the exception must not unreasonably prejudice the legitimate interests of the patent holder (while also taking into account the legitimate interests of third parties). It is within the bounds of this provision that many governments have created legislation to allow for exceptions such as prior user rights or exemptions to infringement for the purpose of compiling data to obtain regulatory approval (commonly referred to as “Bolar” exceptions).

The conditions of Article 30 were analyzed and interpreted in the decision of the WTO Dispute Settlement Body (DSB) in “*Canada – Patent Protection of Pharmaceutical Products*.” In that matter, the European Union brought a complaint against Canada for provisions of its patent law that allowed for manufacturing and stockpiling of pharmaceutical products without the patent holder’s consent [4]. The panel found that whether an exception is “limited” does not depend on the economic impact to the patent holder, but on the level of curtailment of the patent holder’s rights. According to Article 28 of TRIPS, patent holders are entitled to five rights under the patent system – the right to prevent third parties from making, using, offering

for sale, selling, and importing the patented product. The DSB held that the number of rights curtailed is not the determining factor on whether the exception is limited; rather, the extent to which the rights are curtailed must be examined [5]. As a result, the DSB panel found that the “Bolar” exception, when limited to activities related to compiling data for regulatory approval, was a “limited exception” within the scope of Article 30, but that the provision in Canada’s patent law that allowed “stockpiling” exceeded the meaning of “limited exception” under Article 30 [6].

While Article 30 allows for certain limited exceptions to the five rights provided by Article 28 that do not otherwise interfere with the normal exploitation of the patent, it is very narrow in focus. Other exceptions to patent rights, such as compulsory licenses, do not fall under Article 30. In contrast, Article 31 lists several conditions that must be met before a government-authorized use of a patent can occur without the authorization of the right holder. In fact, Article 31 includes a footnote, which further clarifies that the “other use” permitted under Article 31 refers specifically to exceptions other than those permitted under Article 30.

In 2001, during the Fourth Session of the WTO Ministerial Conference in Doha, Qatar, WTO Members adopted a declaration on the TRIPS Agreement and Public Health (the “Doha Declaration”). The text of the declaration reiterates Member States’ recognition of the public health problems facing developing and least-developed countries (LDCs), but also states that the TRIPS Agreement should be “part of the wider national and international action to address these problems.” [7] WTO Members agreed that the TRIPS Agreement allows for certain flexibilities, including:

(5b) Each Member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted.<sup>1</sup>

(5c) Each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency.

In order to address the concern that countries with insufficient manufacturing capacity would be unable to benefit from the compulsory licensing provisions of Article 31, Members adopted the decision on “Implementation of Paragraph 6 of the

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<sup>1</sup>Notwithstanding the inclusion of this provision in the Doha Declaration, at least one WTO member specifically determined that granting a compulsory license for “refusal to license on reasonable commercial terms and conditions empties the substance out of the exclusive rights granted by a patent and protected by the TRIPs Agreement.” See European Communities, “Report to the Trade Barriers Regulation Committee: Examination Procedure Concerning an Obstacle to Trade within the Meaning of Council Regulation (EC) No. 3286/94 Consisting of Measures Adopted by the Separate Customs Territory of Taiwan, Penghu, Kinmen and Matsu Affecting Patent Protection in Respect of Recordable Compact Discs.” (2008), available at [http://trade.ec.europa.eu/doclib/docs/2008/january/tradoc\\_137632.pdf](http://trade.ec.europa.eu/doclib/docs/2008/january/tradoc_137632.pdf).



Doha Declaration on the TRIPS Agreement and Public Health” on August 30, 2003.<sup>2</sup>

The Decision creates certain exceptions to the requirements of Article 31. For example, the requirement under Article 31(f) that a compulsory license is to be granted predominantly for the domestic market is waived for a Member that exports pharmaceutical product under the August 30 Decision.<sup>3</sup> In addition, the requirement for adequate remuneration under Article 31(h) is waived for the LDC or other Member that notifies it will make use of the August 30 decision, as long as the exporting Member, which must grant a compulsory license for export, adequately remunerates the patent holder [8]. Remuneration by the exporting Member country to the patent holder is to be based on the economic value to the importing Member country.

### 3. Examples of legally-deficient compulsory license grants

Despite the reiteration in the Doha Declaration that WTO Members may grant compulsory licenses in the absence of a national emergency, such grants must still comply with the requirements of TRIPS – particularly Article 27 and Article 31. The following section provides examples of national laws or grants of compulsory licenses that have demonstrated a failure to comply with the legal requirements of TRIPS.

#### 3.1. Article 27 – “Without Discrimination . . . Whether Products Are Imported or Locally Produced”

TRIPS Article 27 is explicit in requiring that the patent holder’s right to obtain and enforce a patent must not be contingent on “whether products are imported or locally produced.” As noted below, the “non-discrimination” protections of Article 27 are applicable even in the rare instance that an exception is granted under either Article 30 or Article 31.

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<sup>2</sup>WT/L/540, August 30, 2003. In order to secure adoption of the Decision, a separate statement was delivered by the WTO General Council chair, Uruguayan ambassador Carlos Perez del Castillo (though it is commonly referred to as the “Menon Text,” in reference to Ambassador Vanu Gopala Menon of Singapore, for his role in reaching an agreement that would provide assurance that the Decision would not lead to abuse or weakening of patent rights). The statement can be found at JOB(03)/177, and includes an attachment of “best practice” guidelines.

<sup>3</sup>WT/L/540 at para. 2. According to para. 6(i) of the Decision, if an importing Member is a developing or least-developed country and is also party to a regional trade agreement to which at least half of the members were LDCs at the time of the Decision, the Article 31(f) obligation is further waived to allow the importing Member to export the imported pharmaceutical product to other developing or least-developed countries that are also parties to the regional trade agreement.

## India

On March 9, 2012, the Patent Controller General of India granted a compulsory license to Natco Pharmaceuticals Limited for the Bayer anticancer drug, sorafenib (Nexavar<sup>®</sup>). The decision was appealed to the Intellectual Property Appellate Board (IPAB), which upheld the decision on March 4, 2013. The IPAB decision was further appealed to the High Court of Bombay, which also upheld the compulsory license grant to Natco.

In its arguments to the High Court, the Indian government took the position that a patented product must be manufactured in India in order to satisfy the working requirement of India's patent law. The High Court took exception to this position, stating that "the contention of Union of India that 'worked in India' must in all cases mean only manufactured in India is not acceptable." [9] The High Court nonetheless held that whether importation could satisfy the 'worked in India' requirement would depend upon a sufficient showing by the patent holder as to why the product is not manufactured in India. According to the High Court, this is required by Section 83 of India's Patents (Amendment) Act, 2005, which states that patents "are not granted merely to enable patentees to enjoy a monopoly for the importation of the patented article." The High Court reasoned that this provision of India's national law requires some effort on the part of the patent holder to manufacture the product in India.

In holding that India's national law would allow a finding that importation is insufficient to satisfy local working requirements, the High Court dismissed Bayer's contention that Article 27 of TRIPS prohibits any form of discrimination on the basis of whether a product is imported. The High Court stated, "[s]o far as reliance upon Article 27 of TRIPS by the petitioner is concerned, we find that it ignores the exceptions thereto provided in Articles 30 and 31 of TRIPS." [10] However, this is clearly in contravention of the WTO DSB panel's finding in *Canada – Patent Protection of Pharmaceutical Products*, which held that "in the rights available under national law, that is to say those resulting from the basic rights and any permissible exceptions to them, the forms of discrimination referred to in Article 27.1 should not be present."<sup>4</sup> Thus, there is no basis to argue that the exceptions to patent rights found in Articles 30 or 31 are not still subject to the non-discrimination prohibition found in Article 27.

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<sup>4</sup>Panel Report, *Canada – Patent Protection of Pharmaceutical Products*, at para. 7.91. Interestingly, in taking the position that the exceptions of Article 30 were not subject to Article 27, even Canada acknowledged that the same could not be said of Article 31. Canada conceded that Article 27.1 was meant to prohibit discrimination against products that, prior to TRIPS, were denied patent protection or that were automatically subject to compulsory licenses under national laws – products such as pharmaceuticals. *See para. 7.90.*

## **Brazil**

Brazil's national patent law also includes a provision that permits the grant of a compulsory license on the basis of failure to manufacture the patented product locally. According to Article 68(1) of Brazil's Industrial Property Law No. 9279/1996, a compulsory license may be granted for "the non-exploitation of the subject matter of the patent in the territory of Brazil, by lack of manufacture or incomplete manufacture of the product or, furthermore, by lack of complete use of a patented process, except in the case of non-exploitation due to economic inviability, when importation will be admitted".<sup>5</sup>

On May 30, 2000, the United States sought consultations with Brazil via the WTO dispute settlement procedure, contesting Brazil's local working requirement as a violation of Articles 27 and 28 of TRIPS. The DSB established a panel on February 1, 2001; however, as a result of consultations between the US and Brazil, a settlement was reached. According to the notification of the settlement, the US acknowledged that the law as written had not been applied by Brazil, and Brazil agreed that in return for US withdrawal of its complaint to the WTO, the Brazilian government would hold talks with the US prior to issuing a compulsory license against a US company on the basis of Article 68 [11].

### *3.2. Article 31(a) – "Such Use Shall Be Considered on its Individual Merits"*

According to Article 31(a), each grant of a compulsory license must be considered on its individual merits. The basis for this provision is to effectively prohibit governments from issuing "blanket" authorizations of compulsory licenses. Under a proper reading of Article 31(a), each product, and indeed, each patent covering such product, must be evaluated separately.

## **Indonesia**

In 2012, the government of Indonesia issued Presidential Decree 76/2012, under which multiple pharmaceutical products were compulsorily licensed. The Presidential Decree failed to provide reasoning or justification regarding the need for, or merits of, each authorization. Under the Trade Policy Review Mechanism (TPRM) of the WTO, Indonesia's trade practices were reviewed on April 10 and 12, 2013, at which time Indonesia was questioned about its practice of granting multiple compulsory licenses in a single decree without individual analysis. In response, Indonesia noted that its Patent Law No. 14, 2001 included no provision either allowing or expressly

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<sup>5</sup>The same provision remains in the patent law as amended in 2001 – Law no. 10.196/01, February 14, 2001.

prohibiting the grant of multiple compulsory licenses in a single decree. The government acknowledged that the Presidential Decree authorized compulsory licenses for six antiviral and antiretroviral drugs, “while TRIPs required that the authorization shall be considered on its individual merits,” and further responded that it would examine the obligations of Article 31(a) in view of its existing patent law and current practices [12].

### 3.3. Article 31(b) – “Efforts to Obtain Authorization from the Right Holder”

Before a government can authorize non-voluntary use of a patented invention, the third party in question must be able to demonstrate that efforts were made to obtain a voluntary license on reasonable terms and conditions, and that such efforts were unsuccessful within a reasonable period of time. This requirement can be waived only in the event of a “national emergency” or other extremely urgent circumstance, or when the government authorizes public, non-commercial use of a patented invention. Even if a compulsory license is granted in the event of an emergency, the right holder must nonetheless be notified as soon as reasonably practicable. Similarly, government authorization of third-party use of a patented invention for the public good and for strictly non-commercial purposes also requires the right holder to be promptly informed.

## India

Despite the holding by India’s High Court in the Nexavar<sup>®</sup> case that Natco’s efforts to obtain a voluntary license were sufficient to satisfy the requirement found in Section 84(6)(iv) of India’s Patents Act, the communications between Bayer and Natco would appear to demonstrate otherwise [13]. Natco sent a single communication to the right holder in which it requested a license to produce sorafenib. However, in listing the basis for its request, Natco simply reiterated the provisions of Section 84(1) of India’s Patents Act – the terms under which a compulsory license may be granted under Indian law, which are: (a) failure to satisfy the reasonable requirements of the public, (b) failure to provide the product at an affordable price, or (c) failure to manufacture locally. It is not clear from the High Court decision whether Natco actually proposed terms for a voluntary license. The right holder declined, but also invited Natco to respond with any further information that may be relevant to the request. More than six months after that single communication, Natco subsequently applied for a compulsory license. The High Court decision stated that the mere fact of Bayer’s refusal was sufficient to show that any further efforts by Natco to seek a voluntary license would be unsuccessful. In support, the High Court merely cited to Section 84(6) of India’s Patents Act, which states that a “‘reasonable period’ shall be construed as a period not ordinarily exceeding a period of six months.”

Interestingly, and in contrast to the approach taken by the Controller General and the courts in the Nexavar<sup>®</sup> matter, in a subsequent case, India's Controller General of Patents denied an application by BDR Pharmaceuticals for a compulsory license on the Bristol Myers Squibb drug, dasatinib (Sprycel<sup>®</sup>) [14]. In response to a single communication from BDR, the right holder sought detailed answers to questions about BDR's ability to manufacture and supply the drug, issues of quality control, and other substantive matters relevant to the request. BDR did not respond or otherwise answer any of the questions raised by the patent holder. The Controller General found that BDR's failure to provide any response to these questions, followed only by an application for a compulsory license almost one year later, failed to satisfy the requirement that the applicant make efforts to obtain a voluntary license. The Controller General ruled that BDR's subsequent inaction for almost one year, during which it merely waited for the passage of time, was not sufficient to show that a "reasonable period" under Section 84(6) had elapsed [15].

The plain language of Article 31(b) is clear that authorization of a compulsory license must be preceded by the applicant's efforts to negotiate a voluntary license "on reasonable terms and conditions." The Controller General's decision regarding the corresponding language in India's Patents Act in the dasatinib matter provide strong evidence that the High Court's decision in the Nexavar<sup>®</sup> matter is inconsistent with the requirements of Article 31(b).

## Indonesia

TRIPS Article 31(b) includes an exception to the requirement to seek a voluntary license from the patent holder in cases of a "national emergency or other circumstances of extreme urgency or in cases of public non-commercial use." However, as noted above, even if one of these specific circumstances is invoked, the patent holder must nonetheless be promptly notified.

In issuing Presidential Decree 76 of 2012, the government of Indonesia argued that the blanket grant of compulsory licenses was a "government use" meant to address an "emergency situation." Thus, it argued, the government could issue the decree without making efforts to ensure that a voluntary license was first sought, presumably invoking the waiver of this requirement in cases of "public non-commercial use." [16] However, even assuming this was a case of "extreme urgency" or "public non-commercial use," the government was nonetheless required to notify the right holder of such use.

### 3.4. Article 31(c) – "Scope and Duration of Such Use Shall Be Limited"

TRIPS Article 31(c) requires that the scope and duration of a compulsory license grant must be "limited to the purpose for which it was authorized." Thus, it is incumbent on the granting authority to ensure that such grant is limited in time to address

only the specific condition that prompted the grant. A compulsory license cannot be extended for purposes beyond the specific license grant under which it was authorized.

### **India**

The compulsory license grant for sorafenib by the Patent Controller of India was for the “balance term” of the patent [17]. On appeal, the High Court noted that Section 84(1) of the Indian Patents Act authorizes the grant of a compulsory license if “the reasonable requirements of the public with respect to the patented invention have not been satisfied.” The High Court continued, whether, under Section 84(7)(d), the reasonable requirements of the public are met must be based on working the patented invention “to an adequate extent.” The Court noted that the test for determining what constitutes “adequate extent” would depend on the product for which a compulsory license is sought. For medicines, the High Court noted, “the adequate extent test has to be 100% i.e. to the fullest extent. Medicine has to be made available to every patient and this cannot be deprived/scarified at the altar of rights of patent holder” [18]. The court’s decision suggests that at no time would a compulsory license for a medicine be subject to a review relating to the scope or duration of the license if “the requirement [sic] of all the patients are not being met by the patented drug.” [18] Clearly, the non-discrimination principles of Article 27 would be completely vitiated if Article 31 were interpreted to permit a compulsory license grant on any medicine that was not reasonably available to the entire population of a member country. Thus, the reasoning by which India issued a compulsory license for the duration of the sorafenib patent term would necessarily be inconsistent with the Article 31(c) requirement that the scope and duration of a compulsory license be “limited to the purpose for which it was authorized.”

### **Indonesia**

Indonesia has granted compulsory licenses on three separate occasions – 2004, 2007, and 2012. On each occasion, the grant was for the full duration of the patent term [19]. Presumably, by arguing that the compulsory license grants were based on the need to secure medicines in the interest of public health, the government took the position that such a need would exist for the full term of each of the patents at issue. As in the case of the Indian compulsory license, the government of Indonesia gave no indication that the scope and duration of these compulsory licenses were limited in any meaningful way.

### **Ecuador**

On October 23, 2009, Ecuador’s President Rafael Correa signed Executive Order

118, which authorized a mechanism for government-issued compulsory licenses . The requirements under the Decree are textually consistent with the requirements of Andean Community Law and TRIPS Article 31. However, in practice, compulsory licenses have been authorized for a total of nine medicines thus far [20]. Furthermore, there is no evidence to suggest that the scope and duration of these compulsory license grants were limited [21]. TRIPS Article 31, and in particular Article 31(c), was designed specifically to prevent member states from exercising such extensive curtailment of the rights of patent holders.

### 3.5. Article 31(f) – “Predominantly for the Supply of the Domestic Market”

Because the intent of Article 31 is to provide a mechanism for governments to ensure supply of medicines for their own population, Article 31(f) makes clear that any grant of compulsory license must be authorized *predominantly* for the supply of the market in the Member that granted such license.

## India

The Indian Patent Controller’s 2012 order granted a compulsory license for sorafenib that restricted Natco Pharmaceuticals Limited to making, using, offering for sale, and selling the drug “within the Territory of India” [22]. This is consistent with TRIPS Article 31(f), as well as Section 90(vii) of India’s Patents Act. Despite this explicit restriction, the patent holder was forced to seek an order to prevent the export of generic sorafenib by Natco. On March 26, 2014, the Delhi High Court issued an injunction prohibiting any exports of sorafenib [28]. However, the High Court acknowledged that Natco could petition the court for permission to export sorafenib for purposes of “experimentation and generation of clinical trial data and for submission to the Drug Controlling Authorities” [23]. There is no clear evidence to suggest that Natco planned to export its generic product for purposes other than experimentation or generation of clinical trial data. However, any attempt to export its product for sales in other markets could violate the provision of Article 31(f) if the exports were demonstrated to exceed the amounts supplied by Natco domestically. By requiring Natco to petition the Court before exporting product for clinical trials, the Delhi High Court instituted necessary safeguards to ensure no violation of Article 31(f).

### 3.6. Article 31(g) – “Authorization for Such Use Shall Be Liable... To Be Terminated If and When the Circumstances Which Led to It Cease to Exist and Are Unlikely to Recur”

According to TRIPS Article 31(g), a compulsory license may be terminated if the circumstances leading to the grant of such license no longer exist and are unlikely to recur. While the interests of the authorized licensee must be considered, upon request, the competent authority of any WTO Member granting a compulsory license must review the circumstances under which the grant was initially made.

## Indonesia

As noted above, the government of Indonesia authorized compulsory licenses via Presidential Decree in 2004, 2007, and 2012. The government has indicated that a patentee may request revocation of such grant if the grounds that precipitated the compulsory license were no longer applicable, which would be consistent with Article 31(g). However, the government took the position that the Presidential Decrees were “government use” grants, which, under national law, did not include provisions for a patent holder to request revocation of the compulsory license [24]. Despite Indonesia’s attempt to distinguish between so-called government use and compulsory licenses *per se*, the TRIPS Agreement draws no such distinction. In contrast, each of the provisions of Article 31 is a necessary legal requirement that must be complied with before any Member may grant a third party the right to use a patented invention. As clearly stated in the preamble to Article 31, Article 31 must be complied with when a patent is used without the authorization of the right holder, “including use by the government or third parties authorized by the government.”

### 3.7. Article 31(i) – “Authorization of Such Use Shall Be Subject to Judicial Review or Other Independent Review by a Distinct Higher Authority”

It is to be expected that any decision by a government to undermine the rights granted through its own patent system must be taken with caution. Thus, TRIPS Article 31(i) requires the Member state to provide a mechanism for independent review of such decisions – a protective measure for the right holder. According to Article 31(i), the legal validity of any compulsory license must be subject to challenge via “judicial review or other independent review.” Moreover, such review process must be conducted by a “distinct higher authority” in that WTO Member.

## Indonesia

As noted above, Article 102 of Indonesia’s Patent Law (Law 14, 2001) recognizes two distinct mechanisms for the use of a patent without authorization of the right holder – a compulsory license *per se* and so-called “government use.” According to the government, issuance of a “government use” license or other use of a patent by the government may be authorized in the event of a public health emergency or for defense of the country. As such, the government has argued, such “government use” is “not for commercial purpose.” As a result, the government provides a mechanism for independent judicial review for a compulsory license grant, but not in the event of an authorized “government use.” [25] Under Indonesia’s patent law, only the remuneration rate for such “government use” may be subject to an independent review process – a requirement that is separately found in TRIPS Article 31(j). However, as noted above, the Indonesian government’s attempt to draw a distinction between a



“compulsory license” and “government use” is not supported by Article 31 of TRIPS. It is interesting to note that in the most recent WTO review of Indonesia’s trade policies, the government acknowledged that its laws may need to be amended in view of TRIPS Article 31 [25].

#### 4. Conclusion

Patent rights are granted by governments as a tool to encourage innovation and development. Strong intellectual property protection is essential to ensure that new and innovative medicines are developed and accessible to patients around the world. However, when the same government that grants patent rights subsequently authorizes those rights to be undermined, it is incumbent on the government to ensure that due process is followed, and that the action is proportionate to the need. Furthermore, the use of compulsory licenses must only occur under extremely limited circumstances so as to ensure that the mechanism is not overused or abused. Failure to do so risks eroding the incentives of the patent system, which may ultimately cause delay or denial of patients’ access to innovative treatments. These policy considerations led to the agreement by WTO Members to include the legal and procedural requirements of Article 31. Regardless, the very government that first issued a patent must ultimately be accountable to ensure the rights granted by such patent are respected. A commitment to achieving sustainable access to medicines requires strong political and community commitment [26] and policy coherence [27] between Government agencies and health providers. It is crucial that governments to formulate a long-term strategy, rather than short-term, temporary solutions, which risk undermining a commitment to health innovation and access [28].

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## Patent protection as a key driver for pharmaceutical innovation

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A robust, time-limited system of patent protection is proven to facilitate development of, and access to, innovative pharmaceutical products and processes. In particular, a well-functioning patent protection system is a prerequisite for attracting finance for costly pharmaceutical research, given its high failure rates, by ensuring that successful innovation is rewarded. This article offers a short scientific introduction to current research and development (R&D) in the biopharmaceutical industry before going on to consider the economic role of patent protection, in enabling research through access to capital markets and in accelerating access to new, innovative medicines. In this regard, the article discusses the beneficial economic effects of well-functioning patent systems in regions with restricted access to investors and capital markets. It concludes by underlining the importance of a robust and finely-tuned patent system in contributing to scientific progress and development of new life-saving drugs.

Keywords: Pharmaceutical patents, innovation, research and development

### 1. The role of intellectual property rights in knowledge-based economies

As the world's economies become more knowledge-based, protection of intellectual property rights (IPRs) becomes more important. IPRs are exclusive rights fostering innovation, entrepreneurship, and investment in knowledge-based assets, which ultimately contribute to economic growth by creating the prospect of a return on investment [1] and by facilitating knowledge diffusion.

Patents protect new, technology-based products and processes from being appropriated by third parties, which would dilute the ability of inventors to recoup their investments and to profit from their inventions [2]. The patent system is an incentive system; an exclusive right with economic value is granted for a limited time in exchange for disclosure of the technology that advances the scientific prior art to the benefit of society. It operates at different levels, providing an incentive to invent, disclose, and optimize exploitation efficiency as well as to innovate and diffuse, while providing a tool for governance of markets and firms in a globalized knowledge market economy [3]. Knowledge diffusion [4] is enhanced by the disclosure requirement in the patent application process, which facilitates new collaborations, partnership and licensing arrangements. In this regard, empirical evidence suggests that patent

disclosure increases licensing opportunities [5] and that licensees themselves make significant investments in research and development (R&D) [6].

Disclosure not only reveals the existence of the technology, but also enables a person sufficiently skilled in the art to use the information to make further advances [7]. In essence, the IP system is an exchange between society and inventor in which the grant of exclusive rights potentially sacrifices short-term efficiency gains in order to foster “dynamic long-term efficiency in the form of greater innovation and creativity” [8].

## **2. The importance of patents for the pharmaceutical industry – empirical evidence**

The growing economic importance of patents over the last decades has underscored the role of IP in contributing not only to innovation, but also to competition and trade. In particular, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which is governed by the World Trade Organization (WTO), sets minimum standards for national IP laws, including patent laws. These standards, incorporated into national patent laws according to each country’s requirements, are aimed at facilitating trade among the WTO’s member states.

Two caveats apply to the present discussion. First, the role of patents as a key driver for innovation, though significant for the pharmaceutical industry, cannot be generalized across all sectors. The number of patents granted worldwide has roughly tripled from 400,000 in 1995 to 1.2 million in 2012 [9], but not all industries have been equally innovative or relied on patent protection to secure investment. For pharmaceuticals, however, there is strong empirical evidence that patents have led to the socially desired result of higher R&D spending on developing new life-saving medicines and therapies [10]. Not only have investments increased, but drug approvals also continue to run at high levels; for example, the US Food and Drug Administration (FDA) approved 182 novel medicines between 2011 and early 2016 [11]. Today’s drug discovery and innovative R&D activities take place in an environment of growing complexity, alongside the need for greater resources and incentives for investments in a scientific field with a high failure rate.

Second, patent quality meant not to encompass each and every granted patent, but only those timely granted, providing for legal certainty in the innovation ecosystem. The majority of legal [12] and economic scholars assume such quality if the patent (1) withstands a legal challenge without being invalidated, and (2) “fulfil[s] the key objectives of the patent system, i.e. to reward and incentivise innovation while enabling diffusion and further technological developments” [13], granted without any significant lag [14].

Recent WIPO data show patent filings worldwide increasing by 7–10 percent a year, with China now filing more applications than the US and Japan combined [15]. The rising patent filing trend has been observed for decades, and there is empirical

evidence for a significant impact on the medical innovation ecosystem too, especially for the pharmaceutical industry [16]. Most of the value of today's medicines does not stem from their physical material, but from the continued efforts in research, testing, and innovation required to develop them [17]. So it is not surprising that pharmaceutical and biotechnological patents have the highest indices in studies that aim at measuring both the economic and technological value of patents [18] and their originality [19].

### 3. Understanding pharmaceutical research and manufacturing

Whether patent protection for pharmaceutical products and processes hinders access to innovative medicines is a long-standing and often highly politicized issue between stakeholders, though mainly in a legal and policy context. As stated above, patents promote innovation by providing an incentive to invest in R&D, while they function to structure, define and build innovation partnerships at the same time. Developing new medicines requires high investments in R&D that are essentially speculations on profitable scientific progress to the benefit of mankind. However, the failure rate is high. Unless a few patent-protected commercially-successful drugs are able to recoup investments and generate a profit, finance will dry up and the industry will fail to deliver new drugs.

Before discussing the economic and policy side of pharmaceutical patents, it would be worth having a closer look at the scientific side to see where industry and scientific progress currently stand. It may also be opportune from a pure policy perspective to raise awareness of the scientific complexity of today's R&D and manufacturing. Biologic drugs are complex molecules; they are used as very specific therapeutics that are essential to the health and well-being of patients around the world for diseases which in most cases could not otherwise be treated.

### 4. Understanding the market

#### 4.1. Knowledge-based capital as a prerequisite for gaining access to financing

As both discovery and manufacturing have become more complex and expensive, financing risky R&D has become more difficult, especially since the financial crisis in 2008. Investment appears economically favourable if time-limited patent protection offers the prospect of recouping the investment and generating a profit.

According to a recent OECD study [20], young, innovative companies contribute 17 percent to the job market and a disproportionate 45 percent to job creation. An important success factor is access to financial market instruments; new capital is often relatively difficult to obtain in the absence of a loan history and a traditional

collateral. For young pharmaceutical companies operating in an R&D- and resource-intensive environment, patents can be considered an asset and a positive managerial and technological signal to lenders and investors to provide financing [21]. Even where there is access to financing, asymmetric information, which describes cases in which the investor or lender is not completely able to receive all information for an informed decision, moral hazards, and other specific features of innovation can have the “combined effect of driving interest rates for financing innovation higher than for other types of financing” [22]. These rates can be significantly lowered for companies with a patent portfolio. Innovative companies with IP assets are able to finance projects more easily by obtaining venture capital [23], which is usually accompanied by the introduction of senior management to the company. Investors see exclusive rights, such as patents as potential drivers of profitability and competitive advantage, even though the patented product may still in its early stages of development and need to be further developed and tested for its safety and efficacy.

Furthermore, where there is a functioning secondary market for patents, they can serve as collateral in debt financing and can be sold separately. Policymakers in several countries are currently supporting their IP secondary market, mainly through greater transparency of IP ownership [24] and the creation of new IP market infrastructures [25]. Knowledge-based capital in the form of patents is linked to higher productivity and growth, mainly because the initial costs are not re-incurred when knowledge is used again and because knowledge generates considerable spill-over effects for other sectors [26].

Although it has been questioned whether the patent system can spur innovation and progress in countries with less relevant markets for the pharmaceutical industry [27], patents are assumed to help in gaining access to financing as a prerequisite for local R&D activities that address local needs. However, the value of knowledge-based capital depends on its use, ease of access, level of transaction costs, and extent of protection [28]. In countries without effective IP enforcement, a granted patent alone might not lead to the desired financing, growth, and higher productivity.

#### *4.2. Patents and access to medicines*

As patents are exclusive rights, they do – by nature and design – result in higher prices for a limited amount of time than if the innovation could be directly copied and sold. However, policy discussions on whether patents hinder access to medicines often take place in a context in which, without those patents, the medicines in question would not have been discovered in the first place. At least for essential medicines there seems also to be little evidence that patent protection hinders access to such medicines or treatments; only 8 percent of medicines on the Essential Medicines List of the World Health Organization are patent-protected [29].

Overall, access to medicines is determined by a variety of factors in combination rather than by patent protection alone. Access often depends on the price of a drug, which is in turn influenced by the regulatory system, distribution costs, importer and

supply chain margins, and investment in physicians' and patients' outreach and education [30]; policy factors include taxation, procurement policies, and the use of TRIPS flexibilities. While the availability of these flexibilities has in general facilitated cooperation and can be useful in limited contexts, like health emergencies, their disproportionate use in some cases has resulted in higher prices and delayed availability of new medicines, both ultimately worsening access. Data show that countries with developed IP systems gain access to new medicines earlier than others [31].

However, this finding appears to apply mainly to high-income countries with attractive markets. Significant empirical evidence for the impact of patents on access in developing countries is missing. Currently available studies are mostly inconclusive and the results are not completely understood given the high level of heterogeneity between different countries [32]. For example, one study [33] found that patent regimes accelerate the entry of new treatments for HIV/AIDS in developing countries, but only in those with relatively equally distributed incomes. However, there is also evidence that innovative companies invest in medical education that increases the availability of new treatments to patients in developing countries [34].

Price premiums for patent-protected medicines in developing countries following implementation of the TRIPS Agreement are relatively small; implementation has mostly resulted in higher sales, and better and faster availability of medicines [35]. Contrary to the expectations of some stakeholders, India's implementation of the TRIPS Agreement has not led to high price premiums that could be considered a barrier to access. Although a model study beforehand had predicted a sharp rise [36], the price increase for patented drugs following the Indian reform was 3–5.3 percent overall, 6–12 percent comparing patented drugs and drugs where the application was still pending, and only about 20 percent for patented, newly developed drugs [37]. In comparison, patented medicines in the US market cost on average three times as much as the subsequently marketed generic drug [38]. In addition, one study even suggests that it was India's obligation to comply with TRIPS that transformed several companies' business models from imitation-based to innovation-based [39].

And finally, it should be mentioned that innovative medicines are the basis for the development and later launch of lower-priced generic medicines. By fostering innovation, patents indirectly contribute to making new generic medicines available. Moreover, generic companies in emerging economies are themselves starting to invest in R&D in order to further develop off-patent medicines adapted to local needs. Therefore, it can be concluded that patent protection does not necessarily hinder access to generic drugs, but is an enabler for the existence of generic drugs and furthermore encourages innovation by the generic industry itself.<sup>1</sup>

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<sup>1</sup>One example of such appears to be the Indian generic company Cipla, which refused to provide patent data for the Beall/Attaran study.



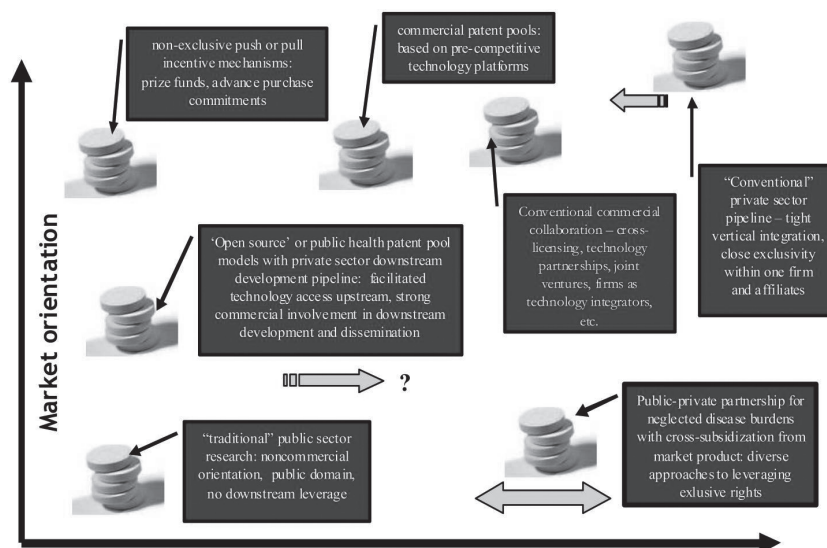


Fig. 1. Source: Taubman, A Typology of Intellectual Property Management for Public Health Innovation and Access: Design Considerations for Policymakers, *Open Aids J*, 4, 2010: 4–24.

#### 4.3. New strategies and models

Most pharmaceutical research is not publicly funded, nor could it all be publicly funded as a public fund could never fund amounts that the capital market can. However, high costs and risks for private investment in pharmaceutical R&D have led research to focus mainly on therapeutic areas with a relevant market for innovative medicines and therapies. This has led to the neglect of some areas by private sector R&D efforts. The World Health Organization, the industry, national authorities, NGOs and other stakeholders have recognized these market failures, especially with regard to neglected tropical diseases (NTDs), and have established several successful collaborations to address this issue, with encouraging outcomes.<sup>2</sup> Nevertheless, some stakeholders advocate a radical change of the current R&D model.

While some proposed measures have their theoretical and/or practical merits, and can complement the current privately funded R&D model, they cannot replace it. From a pragmatic point of view, charitable R&D initiatives, state-directed R&D, and/or public-private partnerships could not sufficiently finance the development of needed innovative medicines in an efficient and sustainable way as through the current capital-market based R&D model (Fig. 1).

No alternative R&D models could replace the private pharmaceutical R&D model with its functioning patent system, without severely affecting the development of

<sup>2</sup>Compare <http://www.ifpma.org/subtopics/neglected-tropical-diseases/>.



new life-saving medicines. The often discussed “de-linkage” of the price for a medicine and R&D costs remains academic as none of the suggested models could provide the continued supply of resources for research as the financial markets do. Especially with regard to NTDs, where market incentives are not available, the further fostering of collaboration between WHO, industry, national authorities and other stakeholders – complementing rather than replacing private-sector funded research – can be expected to continue to produce encouraging results in the future. New models should therefore be seen as complementary, as add-ons to current collaborations, rather than as radical changes to the current innovation ecosystem.

## **5. Conclusion and outlook**

This article aims to raise understanding of pharmaceutical R&D, its economic aspects from a capital-market perspective, and the role of patents as a key enabler for pharmaceutical R&D and innovation to the benefit of patients. Today’s most effective and cost-intensive medicines are protein therapeutics which can only be developed with enormous investment in resources. The growing complexity of both drug discovery and manufacture for such medicines will demand a corresponding increase in the resources needed. This underlines the importance of patents as an incentive and source of growth and innovation. The technological and economic framework in which pharmaceutical R&D takes place requires a finely-tuned patent system that encourages continued scientific progress to combat current and future diseases.

While the analysis of large data sets has shown that the individual value of pharmaceutical patents was slightly declining since 2004 [40] and may continue to decline, patents remain of crucial importance to the pharmaceutical industry to attract investment, and by this, have the means to fail, learn and succeed in the future.

While positive effects of patents on innovation and access to innovative medicines have been observed in countries with developed markets and high GDP, studies in low-income countries are mainly inconclusive and differ considerably between low/middle-income and high-income countries. Although there is no one-size-fits-all approach with regard to IP policy, a well-functioning patent system in accordance with TRIPS as well as a juridical system for enforcement would seem to favour all countries. Given that neither positive nor negative effects for low-income countries have been observed [32], several countries are currently building capacities and adapting their IP laws to stimulate local innovation to join the global trend towards knowledge-based societies. The currently available studies mostly analysed low- and middle-income countries in the process of establishing their IP systems and not their effect after implementation on fostering innovation. It can nevertheless be assumed that implementation of such IP systems will help to address more local health-related issues in the future. The author encourages further empirical studies in this regard to increase the overall understanding of the impact of IP systems on low- and middle-income countries to help formulate more concrete policy recommendations to support creation of an innovation friendly environment.

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## Understanding the pharmaceutical value chain

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Understanding the pharmaceutical value chain requires the identification of each component from manufacturer to end consumer of medicines – and to understand their interaction. In most cases, the manufacturer's selling price represents only a fraction of the retail price of a drug. More than half of the end user price results from insurance, freight charges (CIF), import tariffs and charges, importer margin, distributor margin, retailer margin and taxes.

The article describes the elements of the medicine value chain, outlines factors and costs that contribute to the difference between the net price a pharmaceutical manufacturer receives for a drug and the final amount paid for the drug by the end user. It quantifies the price build-up for specific therapy areas and countries and illustrates the diversity of approaches and costs associated with the value chain through case studies.

Keywords: Pharmaceutical value chain, pharmaceutical distribution and retail margins, pharmaceutical cost analysis

### 1. Introduction

The growing role and use of medicines in healthcare systems globally, driven both by innovative medicines emerging from research and development investments and the expansion of access to meet the imperative of universal health coverage, brings greater importance to understanding the pharmaceutical value chain. This includes the full set of activities that occurs between the point when a medicine is manufactured and shipped from a production or import facility until the time it is received by a patient in the course of their medical care and treatment.

At each step, understanding the specific elements of the value chain, the contribution to the health system that is provided, and the cost components that are incurred provides important context and perspective to the full value that medicines can and do play in advancing population health around the world. However, components of the value chain can and do differ both between and within markets depending on the type of medicine, channel of distribution, reimbursement regulation, or geographic region. Country comparisons underscore the extent to which health systems differ in a multitude of ways and for many reasons.

Recent research on this topic focused on seven markets, representing a range of income levels, health system development and geographic regions, and comprised the Netherlands (a high income country with a rational approach to pricing and margins

that is useful as an “anchor” country for comparison purposes), Brazil, India, Indonesia, Kenya, Russia and South Africa [1]. The researchers also selected five therapy classes representing a mix of chronic and acute disease areas, and comprised antibiotics, diabetes, epilepsy, hypertension and respiratory. For each therapy area and in each country, analysis of costs, margins and mark-ups was undertaken, indexed to 100 and represented in a way that enables comparison.

## 2. Major components of the pharmaceutical value chain

In advancing the understanding of the pharmaceutical value chain, it is useful to look at three major components:

1. **Manufacturing of the medicine:** In order to produce a medicine, a number of steps are involved, from the initial research and development phase, to gaining regulatory approval which allows a medicine to be sold in a market, to the final commercialization phase. The specific steps and requirements will differ between types of medicine, manufacturers and countries.
2. **Distribution to the dispensing point:** This step includes the transportation and handling of the medicine from the manufacturer to the end user, whether this is a retail pharmacy (retailer), hospital or dispensing doctor. The complexity of this journey will differ depending on manufacturer location, the need for importation of the medicine, the nature of special handling requirements, and the geographic location of the end user which will vary between large urban centers and remote rural villages.
3. **Dispensing to the end user:** Providing the correct medicine dosage and form, to the right patient, in a convenient and timely manner is the final step in the value chain. This step can also involve a number of additional activities, including checking for potential interactions, providing advice, and processing reimbursement claims, each of which is intended to ensure the patient receives the full benefit and value from the medicines they receive.

In each of these components of the value chain, a range of costs are incurred and value added, as summarized in Fig. 1.

## 3. Activities, costs and value added in manufacturing medicines

Broadly speaking, there are two categories of manufacturing required for drug production: active pharmaceutical ingredient (API) manufacturers which produce the raw ingredients used in medicine; and finished form manufacturers which produce the final product to be sold to market and consumed by the patient.

Finished form manufacturers can also be categorized as innovators or generic companies. Innovator companies invest in research and development in order to discover

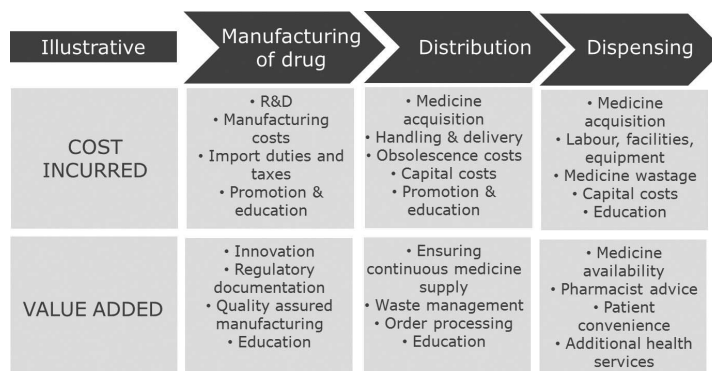


Fig. 1. Costs incurred and value added in components of the pharmaceutical value chain.

and bring new medicines to market. Due to the large financial investment involved, these medicines receive a period of market exclusivity. At the point this expires, generic manufacturers are able to manufacture and bring to market generic versions of the original brand molecule which contain the same active substance, produce the same therapeutic effect and are manufactured to the same quality as the original product.

For originators, the largest costs are associated with drug discovery, which identifies new chemical or biologic entities that have the potential to advance the current standard of disease treatment, and the costs of subjecting potential drug candidates to rigorous testing through clinical trials, which many will fail to complete. Additional costs are incurred in the submission of applications to regulatory agencies, and once approved, costs are incurred by manufacturers to promote and educate key stakeholders about the product and the benefits it can bring to patients. It is difficult to put an exact figure on the cost involved in bringing a medicine to market, as this will differ between the type of drug, level of innovation and magnitude of risk involved [2]. In contrast, generic manufacturers normally have relatively low development and manufacturing costs. Their main means of promotion is through trade incentives, offering larger discounts to secure volume sales.

The value added from the generation of a new medicine is first and foremost that which directly relates to patient treatment. Such advances may tackle a new disease or indication, improve health outcomes, treatment safety, tolerability and/or side effects and the ability to better treat specific patient sub-populations. In addition, there are wider benefits to the health system such as decreasing the burden on other health resources and overall societal benefits such as enabling people to return to work.

The value added from generic manufacturers is that of introducing competition into the market, which in an efficient market can help payers achieve savings on older treatments in order to invest in new ones or offer lower cost alternatives to patients in out-of-pocket markets.

## 2013 value weighted average across five therapy areas

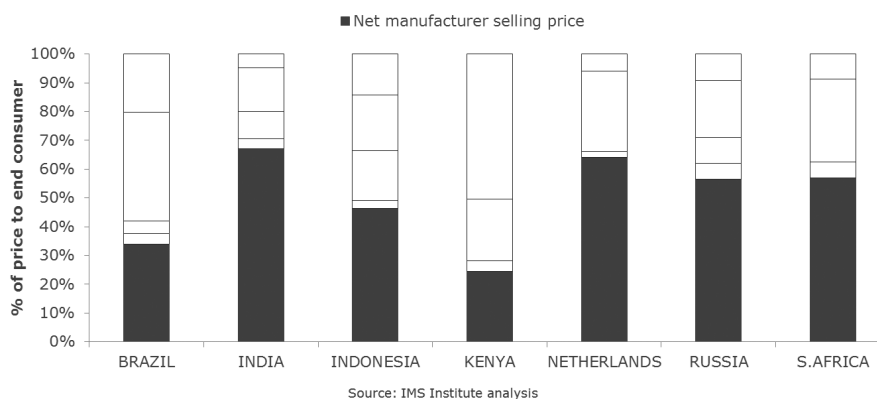


Fig. 2. Net manufacturer selling price compared to end consumer price.

Unlike prices for other products, medicine prices are determined by pricing policies which are unique to each country. For example, in Russia the maximum ex-manufacturer price for drugs on the essential drugs list is based on product type and whether the product is manufactured in Russia. In contrast, in Brazil, trade and end user prices are regulated and the price at which the pharmacy purchases medicine (plus VAT) must not exceed this regulated trade price, leaving wholesalers to negotiate their discounts with the manufacturers. The official (regulated) or negotiated price however, is not always the price that the manufacturer receives. There are a number of factors which impact the level of a manufacturer's net price. One of the largest is trade discounts which are offered by manufacturers to wholesalers or pharmacies and are negotiated in business to business transactions. These discounts vary in size depending on the purchasing power of the buyer and level of competition, but as a general rule of thumb generic manufacturers often offer much larger discounts in order to secure volume share. For example in Brazil generic manufacturers may offer discounts of over 50% from list prices, while originators may offer discounts in the range of 10–15% [3].

#### 4. Manufacturer costs relative to end user price

Manufacturer costs relative to end user price vary widely across the countries studied, and range from 24% in Kenya, to over 64% in the Netherlands, as shown in Fig. 2. At an individual therapy class level, the range was also significant in certain countries. For example, in Brazil the average for antibiotics was 31% of end user price, but 42% for respiratory drugs, while the Netherlands saw the widest variation with 38% for antibiotics and 78% for respiratory. There can also be differences in total therapy drug costs based on the mix of different types of drugs which have different costs relative to end user price.



## 5. Activities, costs and value added in distribution of medicines

The distribution of medicines in most markets is carried out by importers and wholesalers, which act as a link between manufacturers and retailers to ensure the continuous supply of medicine, regardless of the geographical location and portfolio of medicine required. For those medicines which are imported, there is often an additional step in handling the logistics of bringing the medicine into the country. The exact number of steps, participants and complexity in the distribution component differs based on the nature of the products, markets and distribution profile.

Pharmaceutical distribution needs to meet the logistical challenge of serving a large number of pharmacies with products sourced from many manufacturers and often in a short period of time. At the same time regulation may require a certain level of distribution standards to ensure that medicines are handled according to good distribution practice. The distributor invests in inventory to be able to service its customers. The distributor might typically be holding one to two months' worth of inventory and the cost to carry inventory includes warehousing cost, capital cost, and obsolescence. The working capital, both for the inventory held and supply stock to pharmacies, is done on a credit cycle which can range from 28 days in the Netherlands to 120–150 days in Kenya (90 days to get paid by the retailer and two months of stock holding) [3]. For the wholesaler this results in additional costs from interest and the risk that pharmacy repayment may be delayed or in a worst case scenario, default on their obligations. Furthermore, in countries such as Kenya, the importer is unlikely to pay for goods with domestic currency and will be impacted by the financial cost of acquiring foreign currency and any fluctuations in exchange rate when purchasing medicines from manufacturers.

The key function of a wholesaler is to resolve the challenge of being able to meet varied and un-predictable patient needs, by supplying medicines from manufacturers, without requiring the retailer to hold large inventories on-site. A second major function (and cost) is to provide the necessary working capital for pharmacies to allow them to purchase the required drugs, before receiving end user payment. Finally, in some markets wholesalers provide a broad set of commercial support to independent pharmacies to improve the operation of the business, such as category management (retail initiatives to help grow the pharmacies business), sales training, accounting and continuing education for pharmacies.

Distributors are traditionally paid on a regulated margin basis set as a fixed percentage of the price. In some countries, this has become a regressive margin with a lower percentage applied for more expensive packs. In markets with regulated margins, discounts from the manufacturer might also exist; in other countries and for some categories of products, discounts may not be allowed. Generally, discounts are given when the wholesalers can influence which manufacturer's product is sold, meaning that they are more common on products without patent protection (no longer protected originals or generics). Some countries have moved to a "fee-for-service model" in which the margin for the wholesaler is negotiated between the distributor and the manufacturer.

## 2013 value weighted average across five therapy areas

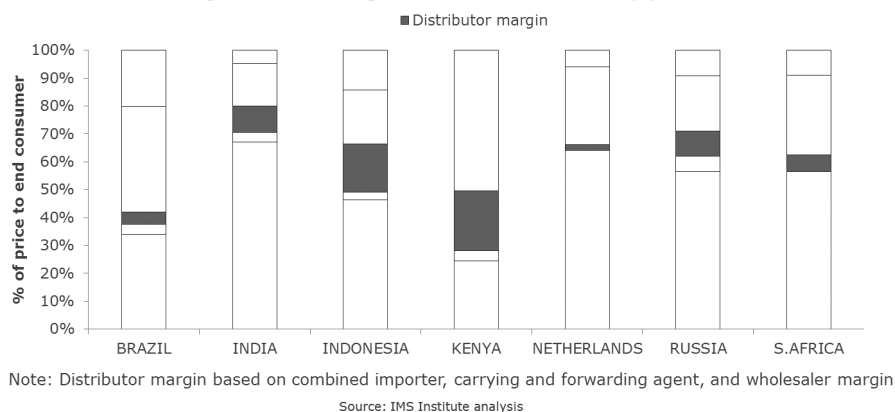


Fig. 3. Distributor margin compared to end consumer price.

## 6. Distribution costs relative to end user price

Across countries the total distribution margin can vary from 2% of the end user price in the Netherlands to 22% in Kenya (see Fig. 3). There may however, be a need for these types of differences. For example longer payment cycles for pharmacies in Kenya and a greater reliance on labor force versus wholesalers in the Netherlands means that operating and labor costs are likely to be substantially higher. Some Kenyan wholesalers will run call centers to deal with pharmacy orders, while in the Netherlands much of this is automated. In India, under the Drugs Price Control Order 2013, both the wholesaler and retailer margins are differentially regulated based on essential drug classification, with maximum margin for distributors at 8% for scheduled drugs and 10% for non-scheduled drugs. In Russia, distributor margins are regulated for products on the essential medicine list and differ according to the geographic location in which the medicine is purchased, as regional authorities are required to calculate maximum mark-up for both wholesalers (and retailers) for products on the essential drugs list.

## 7. Activities, costs and value added in dispensing to the patient

Retailer remuneration is determined by two key factors. Firstly the level of discounts negotiated from the wholesaler, which determines the acquisition cost of the medicine. Secondly, the margin made on the acquisition cost of the medicine paid by the end user. Mark-up/margin can be set by free pricing, a regulated fixed percentage of the acquisition cost and/or a regulated fixed dispensing fee. The most common method of regulation used in the markets studied was the percentage mark-up/margin model. South Africa uses a mixture of a fixed and percentage variable

component, while the Netherlands is the only country where remuneration is a fixed fee per prescription (regardless of the number of packs dispensed) [4].

Retailer costs can be split into those which are fixed and those which vary depending on the level of business. Fixed costs include the cost of labor (pharmacist, etc.), facilities, equipment (including information technology), utilities and insurance. Variable costs include product acquisition cost and the volume being purchased; medicine wastage resulting from expiry or damage; and the capital cost of inventory. The costs of running a retailer in a rural location compared to an urban area can be quite different. The size of a retailer in a rural location is often much smaller, clientele is scarcer and often poorer, both of which reduce the opportunity to recover fixed costs [5].

One fundamental role of a retail pharmacist is that of logistics: being able to dispense the right drug, to the right time at the correct dosage. This in itself is an oversimplification as this task also entails correcting prescribing errors, processing the prescription, labelling etc. and advising and educating patients on the safe use of prescribed drug, contraindications, interactions and side effects. For example, some pharmacists in the Netherlands suggest that 15% of prescriptions require an intervention from the pharmacist, e.g. adjusting dose to patient weight, change of label due to preference etc. [6]. Pharmacists can also spend a substantial amount of time mitigating the impact of drug shortages by finding either new sources or alternative medicines.

As retailer business models evolve, additional services are becoming more common and the role of a pharmacist is no longer just about medicine provision, but the provision of services which help maintain patient health [7]. These can include training on the administration of medications including inhalation and injectables, blood pressure testing and measurement of blood glucose and triglyceride levels, education on disease management through non-medical means such as nutrition and other lifestyle factors, and improving patient adherence through education and patient monitoring [8]. Such initiatives have the potential to improve patient health outcomes and reduce health service utilization, which can ultimately reduce the burden on the overall health system.

Retail dispensing fees in many of the markets analyzed – Brazil, India, Russia and South Africa – are capped to help regulate the end-consumer price. However, to differentiate themselves from competition, pharmacies may charge below this maximum either by foregoing or reducing the dispensing fee (South Africa) or passing on discounts acquired from the wholesaler to the patient (Brazil) [3]. This means that the prices of drugs are often well below the official regulated end user price. However, the ability to discount varies between types of pharmacies. Those which are able to negotiate high discounts from wholesalers – normally the large chains – are subsequently able to offer cheaper prices to patients than smaller independent pharmacies which are unable to run on smaller margins.

In some markets where retailers make a loss from selling prescription medicine, profit is instead generated from additional over-the-counter and health and beauty

## 2013 value weighted average across five therapy areas

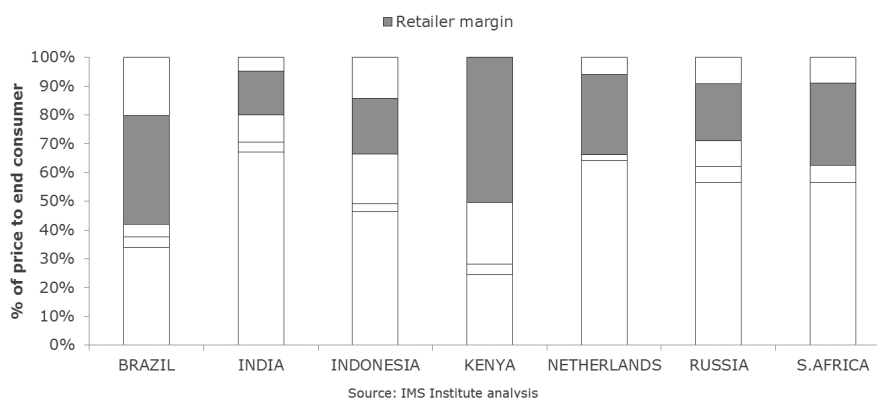


Fig. 4. Retailer margin compared to end consumer price.

sales. An alternative business model finds other retailers which are very much focused on prescription drug dispensing to drive their business profitability.

### 8. Retailer costs relative to end user price

The average level of retailer margin ranges from 15% of end user price in India to 50% in Kenya (see Fig. 4). The magnitude of retailer margin can also differ between therapy area and product types depending in part on the level of regulation or negotiation that retailers have with wholesalers and manufacturers.

For example, in Brazil in 2012, wholesalers on average provide discounts to pharmacies of approximately 60.4% of the regulated trade price for generics, 30.3% for branded originals, and 16.2% for off-patent branded originals [9]. Similarly, in the Netherlands, the implementation of a fixed dispensing fee means that in areas where there are largely patented protected brands, these more expensive medicines make up a smaller proportion of the total price build-up, compared to their lower cost generic counterparts. In South Africa, where there is a combination of chain and independent pharmacies, differences in the price build-up can vary drastically. While there is a maximum margin in place, for larger chains a lower price can be offered to patients without negatively impacting business viability [10]. Furthermore, while trade discounts are prohibited in South Africa, logistics providers pay fees to the pharmacy under the guise of 'marketing fees' and 'data fees' which act as incentives to purchase from certain logistics providers, or to stock certain manufacturers' products as priority. The Department of Health is currently proposing to ban such practices, as well as reviewing retailer dispensing fees to help adjust for the loss retailers receive from such practices.

Country <sup>(i)</sup>	Customs duty rate <sup>(ii)</sup>		National sales tax
	Finished form products	Active pharmaceutical ingredients	
Brazil	9.8%	9.5%	Average 18%
India	10%	10%	Average 5%
Kenya	10%	0%	0%
Indonesia	4.3%	4.2%	10%
Netherlands	0%	0%	6%
Russia	10.2%	0%	10%
South Africa	0%	0%	14%

(i) Latest data available for each country

(ii) Most favoured nation (MFN) duty rate is that which each country has agreed to offer all countries which are members of the World Trade Organization (WTO). Countries with other trade agreements in place may have rates in place that are lower than the MFN. The rates stated in this table are an average of all ad valorem duties under the HS code 3004 for finished form pharmaceuticals and 3003 for APIs. Any conclusions based on this data are the responsibility of the authors and do not necessarily represent the opinion of the WTO.

Source: World Trade Organisation, September 2014. [Online]. Available: <http://tariffdata.wto.org>

Fig. 5. Medicine import tariffs and national sales taxes.

## 9. Government tariffs, taxes and charges relative to end user price

Taxes have been shown to be one of the larger components contributing to the price build-up of medicines [11,12]. The most prominent of these in certain markets is the import tariff, which is a customs duty imposed by importing countries on the value of goods brought in from other countries. Import duties are used to raise government revenues and help domestic producers by providing a price advantage versus international competitors. Another form of taxation is medicine sales tax, commonly in the form of value-added tax (VAT). Similarly to import tariffs, VAT is applied in different magnitudes between countries and can be applied at both a national and state level. Figure 5 summarizes the import tariffs and national sales taxes applied in each market. In addition there are many examples of country specific taxes charged.

Across countries the level of total government tariffs, taxes and charges can vary from 6% of end user price in Kenya to 24% in Brazil. Aside from Kenya, where sales tax in general does not apply to medicine (there are some exceptions to this rule), tax is the larger of the two components (see Fig. 6). Variation in the impact of taxes and tariffs between countries occur because of different approaches taken by governments to raising revenue and different mixes of business that attract these costs. For example, tariffs applied to imported goods but not to domestically manufactured goods can have a large impact on the overall cost structure in a country. In India, import tariffs contribute about 11% of the end user price for international manufacturers' products but do not impact products sourced from the domestic production of API's and finished form products.

### 2013 value weighted average across five therapy areas

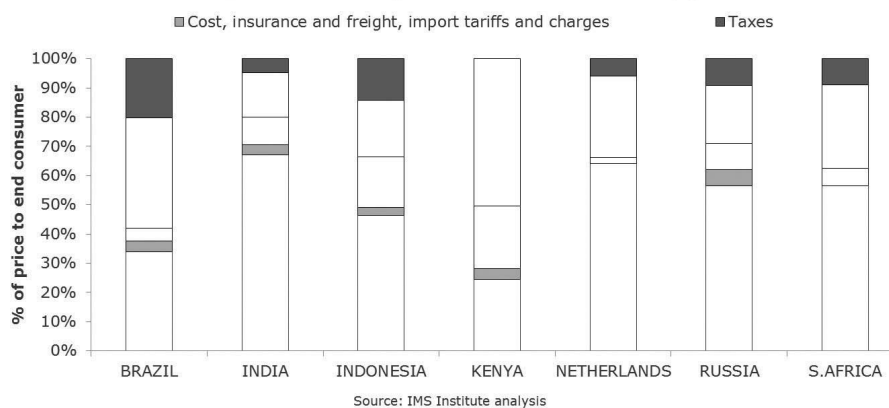


Fig. 6. Government taxes, tariffs and charges compared to end consumer price.

## 10. Discussion

Understanding the relative magnitude of price components along the pharmaceutical value chain is essential to inform the discussion of affordability and access to medicine issues. By analyzing the components of the pharmaceutical value chain in specific countries and for specific therapy areas stakeholders can better establish a basis of common understanding and evidence.

The analysis presented here illustrates vividly the wide variation by country of the average contributions of manufacturer costs, distributor margins, retail margins and government tariffs, taxes and charges relative to the final end user price (see Fig. 7). These averages are weighted by product type and therapy area based on actual use mix, and therefore also reflect the weighted impact of diverse policies and practices across the value chain in these countries. They are not intended to represent all medicines in each country, but are based on analyzing the best available objective and quantified information for a defined set of therapy areas, supplemented with local market expertise and engagement with each of the major stakeholders.

Across the value chain, the level of discounting is a complex, but necessary factor to consider in this type of analysis, especially when it is used to inform policy decisions. While it is not feasible to factor in discounts product by product due to the confidential nature in which they are set, it is possible to use industry insight to estimate the level of discounting that occurs along the medicine value chain. The gross manufacturer price or visible wholesaler/retailer margins are often not reflective of the true price received. A full understanding of the realities of margins and prices is necessary to ensure that policy-making aimed at adjusting margins and prices does not inadvertently reduce or eliminate the viability of a particular stakeholder continuing to do business in that market. This may particularly be the case when local

## 2013 value weighted average

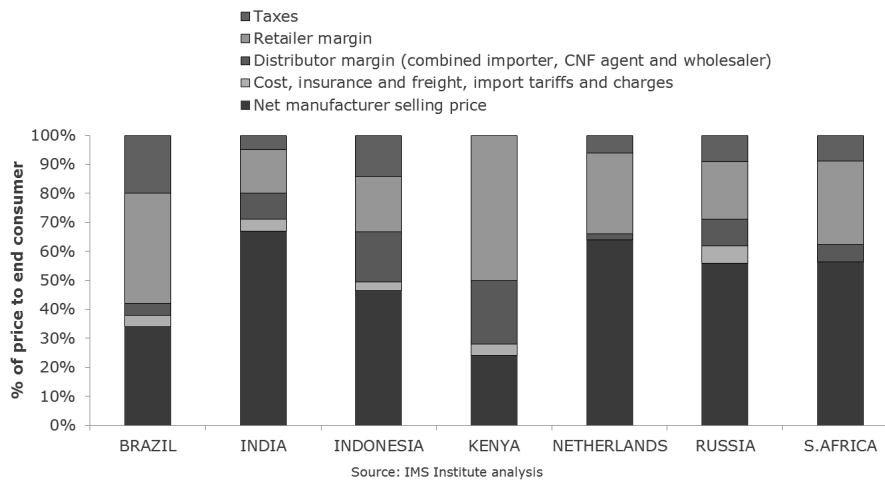


Fig. 7. Price build-up across five therapy areas.

environmental factors are considered, such as the additional costs required to provide specific types of medicine or to provide reliable supply to rural areas.

Ultimately, policies need to strike a balance between maintaining the long-term vitality of each component of the value chain, and making medicines available and affordable to patients. Furthermore, there is scope in many countries to capitalize on the value that each stakeholder is already bringing to the healthcare system, and exploring how efficiencies can be gained in the overall system rather than pursuing a narrow focus on the cost of medicine or one particular element of the value chain.

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## Breaking New Ground: The WTO Agreement on Trade Facilitation<sup>1</sup>

*Potential and Perspectives for the Pharmaceutical Industry*

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Recently adopted, the WTO Agreement on Trade Facilitation (TFA) adds fresh momentum to worldwide efforts to speed up the movement, release and clearance of goods across borders. With all required decisions having now been taken in Geneva, preparations are under way to ensure the Agreement's expeditious entry into force. Once in operation, this ground-breaking treaty will significantly accelerate cross-border trade and reduce related costs.

This article analyses the TFA from a pharmaceutical angle, highlighting provisions of particular interest to the industry. It will look at how the new Agreement is likely to impact trade in medical goods and where business stands to benefit. A final segment will review governments' implementation plans and discuss the road ahead.

Keywords: Cutting red tape, expedited clearance, perishable goods, pharma trade, trade facilitation, ratification, WTO Agreement on Trade Facilitation, WTO negotiations on Trade Facilitation

### 1. Setting the stage

When Chairman Gita Wirjawan hit the gavel at the WTO's Ninth Ministerial Conference in Bali to signal the conclusion of the trade facilitation (TF) negotiations, it was met with enthusiasm, but also relief. The decision marked the end of an undertaking that had occupied the WTO's membership for almost a decade and which some had begun to fear might never actually be accomplished.

In addition to ending the TF talks, ministers set out a road map for implementing the new Accord and mandated related preparatory work, which commenced shortly afterwards. Two and a half years on, major milestones have been met and the Agreement is close to entering into force. It will usher in a new era of trade facilitation reforms and substantially expedite cross-border trade.

The article examines how the new treaty will impact the operations of the pharmaceutical industry and traders more broadly. It will identify the provisions most

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<sup>1</sup>The views expressed in this article are those of the author alone and do not necessarily reflect the views of the World Trade Organization.

relevant for pharma trade and analyse their likely impact on the pharmaceutical sector. A look will also be taken at where we stand with respect to putting the new Agreement into force.

## 2. Great expectations

Expectations for the Trade Facilitation negotiations were high from the outset. Launched in August 2004, they were hailed as a “*truly historic achievement*.”<sup>1</sup> Reference was made to them as “*the pillar [of the multilateral trading system] that had been lacking*”<sup>2</sup> and as an exercise that would “*affect the welfare of farmers, factory workers, small business people and other producers, consumers and their dependents in all countries*.”<sup>3</sup>

The sizable benefits of a WTO Agreement on Trade Facilitation had already been highlighted when Members were debating the terms of a negotiating mandate. Top on the list were cost savings, both in terms of trade transaction- and administrative costs. A strengthened tax and revenue base, together with reduced losses from corruption, were equally sighted as tangible monetary benefits. References were also made to non-financial gains of an agreement, such as enhanced control and enforcement of regulations, an improved investment climate and increased participation in cross-border trade.<sup>4</sup>

## 3. Trials and tribulations

Despite widespread agreement on the benefits of trade facilitation reforms, the road to the TFA turned out to be a lengthy one. It took a long time to get to the point where the talks could even start: governments needed almost 8 years to move from a first work mandate to the beginning of rule-making, and trade facilitation was only added to the Doha Round after a 3 and a half year delay.<sup>5</sup> The fact that the talks already involved almost 150 Members when they started and were an integral part of a much larger round of negotiations – the Doha Development Agenda – that included almost two dozens of issues, made the environment challenging enough. Added to this was the fact that decisions on trade facilitation, like all WTO negotiating exercises, had to be taken by consensus at every step of the process.

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<sup>1</sup>Statement by Supachai Panichpakdi, WTO Director General at that time.

<sup>2</sup>Statement by Bolivia at the General Council meeting where the decision to launch the TF negotiations was taken. (WT/GC/M/87, paragraph 153.)

<sup>3</sup>Statement by Jamaica (WT/GC/M/87, paragraph 126.)

<sup>4</sup>For an overview of the most frequently arguments made, see a submission by the European Communities (WTO document G/C/W/143).

<sup>5</sup>WTO Members needed more time to agree on the negotiating modalities.

Despite these challenges, the TF negotiations were able to get off to a good start and quickly made up for lost time. While subsequent delays and missed deadlines – usually because the pace of the TF process was tied to the broader, slower moving, and more contentious Doha Round – extended their overall duration beyond initial targets, the trade facilitation talks continued to progress and were ultimately even the first large Doha negotiating dossier to make it to the finishing line.

#### 4. What's on the table?

The final text seeks to expedite the movement, release and clearance of goods<sup>6</sup> in several ways. In line with the negotiating mandate, the Agreement builds on the existing legal framework, especially parts of the General Agreement on Tariffs and Trade (Articles V, VIII and X of the GATT, dealing with publication and administration of trade regulations, fees and formalities connected with importation and exportation and freedom of transit, respectively).

A common thread running through virtually all provisions is the attempt to increase transparency and predictability and to reduce discrimination. Many also seek to improve cooperation and coordination.

Most provisions address the trading community in its entirety and cover goods in broad terms. Others have a more specific focus, and therefore a more limited scope. The vast majority of both categories should be of interest to the pharmaceutical industry.

The **first article** of the Agreement seeks to improve access to information, calling for the prompt publication of a series of data<sup>7</sup> in a non-discriminatory and easily accessible manner. Members are further asked to make information available through the internet and to establish enquiry points to answer queries from interested parties – together with the required forms and documents.

**Article 2** mandates opportunities for traders to comment on the proposed introduction/amendment of relevant laws and regulations (which further have to be published as early as possible before their entry into force.) In addition, each Member has to provide for regular consultations between its border agencies and traders/other stakeholders.

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<sup>6</sup>The coverage also extends to goods in transit. For details, see WT/L/579.

<sup>7</sup>The article mentions (a) procedures for importation, exportation, and transit (including port, airport, and other entry-point procedures), and required forms and documents; (b) applied rates of duties and taxes of any kind imposed on or in connection with importation or exportation; (c) fees and charges imposed by or for governmental agencies on or in connection with importation, exportation or transit; (d) rules for the classification or valuation of products for customs purposes; (e) laws, regulations, and administrative rulings of general application relating to rules of origin; (f) import, export or transit restrictions or prohibitions; (g) penalty provisions for breaches of import, export, or transit formalities; (h) procedures for appeal or review; (i) agreements or parts thereof with any country or countries relating to importation, exportation, or transit; and (j) procedures relating to the administration of tariff quotas.

Transparency, predictability and due process goals underpin the Agreement's subsequent provisions (**articles 3–5**), mandating advance rulings, procedures for appeal or review and other measures to enhance impartiality and non-discrimination.

**Article 6** sets out several disciplines on fees and charges imposed on or in connection with importation and exportation, seeking to reduce their number and diversity. Members are also restrained in their ability to impose penalties for a breach of their customs laws, regulations or procedural requirements.

The next article – **7** – is of special significance for the pharma industry. It contains a series of measures to facilitate the release and clearance of goods. The first sets out provisions on pre-arrival processing (article 7:1), calling upon each Member to “*adopt or maintain procedures allowing for the submission of import documentation and other required information, including manifests, in order to begin processing prior to the arrival of goods. . .*”. Members shall further “*provide for advance lodging of documents in electronic format for pre-arrival processing of such documents.*”<sup>8</sup> Provision is also made for electronic payments. According to article 7:2, “*Each Member shall, to the extent practicable, adopt or maintain procedures allowing the option of electronic payment for duties, taxes, fees, and charges collected by customs incurred upon importation and exportation.*” The next segment – article 7:3 – calls for the separation of release from final determination of customs duties, taxes, fees and charges. It is followed by language on risk management, mandating Members to adopt or maintain related systems for customs control (article 7:4).<sup>9</sup> Article 7:5 requires the adoption (or maintaining) of post-clearance audit to ensure compliance with customs and other related laws and regulations. Members are further “*encouraged to measure and publish their average release time of goods periodically and in a consistent manner*” (article 7:6). Article 7:7 sets out provisions for authorized operators, calling upon each Member to provide “*additional trade facilitation measures related to import, export, or transit formalities and procedures (. . .) to operators who meet specified criteria*”. They are further required to “*adopt or maintain procedures allowing for the expedited release*” of specified goods<sup>10</sup> (article 7:8).

The last segment of the article – 7:9 – deals with perishable goods and is of particular relevance to the pharma industry. Based on a proposal first presented by Australia, Brazil and New Zealand [1], all WTO Members are mandated to give special treatment to this kind of merchandise, defined as “*goods that rapidly decay due to their natural characteristics, in particular in the absence of appropriate storage conditions.*”<sup>11</sup> In specific terms, Members are obliged to “*provide for the release of*

<sup>8</sup>There is a built-in qualification according to which this has to be done “*as appropriate*”.

<sup>9</sup>The provision contains a qualification according to which this should be done “*to the extent possible*”.

<sup>10</sup>The article states that this should be done for “*at least those goods entered through air cargo facilities to persons who apply for such treatment*”.

<sup>11</sup>Article 7:9 of the TFA, footnote 10. Attempts to come up with a specific list of covered products failed to generate the necessary consensus. The implication for pharmaceutical goods is that some products will fall within the definition, while others will not.

*perishable goods: (a) under normal circumstances within the shortest possible time; and (b) in exceptional circumstances where it would be appropriate to do so, outside the business hours of customs and other relevant authorities*” [2]. Each Member is further requested to “*give appropriate priority to perishable goods when scheduling any examinations that may be required* [3].” There is also an obligation to “*either arrange or allow an importer to arrange for the proper storage of perishable goods pending their release.*”<sup>12</sup> In cases of significant delay in the release of perishable goods, the importing Member is required – upon written request – to provide a communication on the reasons for the delay. Flexibility with the execution of this obligation is provided by the qualification of that having to happen “*to the extent practicable* [4]”.

This proposal had been introduced at a late stage of the negotiating process – indeed, it was one of the last provisions to be added to the text – but received a very positive response. Virtually all delegations supported the idea of special treatment for perishable goods. What took a few months to negotiate were the specifics of how that objective should best be secured. The consensus principle of the decision-making process required Members to find compromises. Several of the initial ideas had to be dropped,<sup>13</sup> but essential elements were retained and made it into the final text. The ultimately agreed language still reflects the different interests that had to be balanced. This can already be seen in the opening paragraph, which sets out the basic objective of the provision – the prevention of avoidable losses or deterioration of perishable goods – but then goes on to state that measures to achieve that end could only be introduced “*provided that all regulatory requirements have been met.*” Nevertheless, the core of the original proposal survived and promises to improve trade in those goods noticeably.

**Article 8** seeks to encourage border agency cooperation, both within a given country and in dealing with agencies of neighbouring Members with whom a common border is shared.

It is followed by a call to “*allow goods intended for import to be moved within a territory under customs control from a customs office of entry to another office from where the goods would be released or cleared*” (**article 9**).

**Article 10** sets out a series of measures to cut back on formalities connected with importation, exportation and transit of goods. It calls for such formalities – and documentation requirements – to be reviewed with a view to minimizing their incidence

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<sup>12</sup>Article 7:9 of the TFA, paragraph 3. The Member may require that any storage facilities arranged by the importer have been approved or designated by its relevant authorities. The movement of the goods to those storage facilities, including authorizations for the operator moving the goods, may be subject to the approval, where required, of the relevant authorities. The Member shall, where practicable and consistent with domestic legislation, upon the request of the importer, provide for any procedures necessary for release to take place at those storage facilities.

<sup>13</sup>See, for instance, the suggestion to allow for consignments of perishable goods to be cleared at the premises of the importer or at the premises of a third party designated by the importer.

and complexity (article 10:1). Members are further asked to accept copies of documents required for import, export, or transit formalities (article 10:2) and encouraged to use international standards as a basis for those formalities and for related procedures (article 10:3). The Agreement also aims to establish 'single windows' in countries, although the related language had to be phrased in best endeavour terms (article 10:4). Practices like preshipment inspection and the mandatory use of customs brokers are subjected to disciplines (articles 10:5 and 10:6). Members are further obliged to apply common customs procedures and uniform documentation requirements for release and clearance of goods throughout their respective territories (article 10:7<sup>14</sup>). Where goods presented for import are rejected on account of their failure to meet prescribed sanitary or phytosanitary regulations or technical regulations, the Member shall, subject to and consistent with its laws and regulations, allow the importer to re-consign or to return the rejected goods to the exporter or another person designated by the exporter (article 10:8). The last component of the article calls for each Member to allow for the temporary admission of goods and for inward and outward processing (article 10:9).

**Article 11** sets out a series of requirements to improve the conditions for free transit of goods. They include measures to reduce fees, charges and formalities, and to enhance non-discrimination.

The last article (**12**) prescribing TF reforms seeks to enhance the exchange of information between customs administrations for the purpose of verifying an import or export declaration.

## 5. Expected impact

Collectively, these measures are expected to have a considerable impact on several levels. Some effects were already being felt even before the negotiations had finished. The launch of the TF talks – and the resulting international focus on the issue – triggered an increase of facilitation reforms. An analysis of TF provisions in regional trade agreements (RTAs), for instance, showed a noticeable rise in their frequency after 2004 [5]. There was also a significant impact on the content side, with more and more TF measures being modelled on the TFA [5].

Most analyses of the benefits of the TFA start with the expected economic gains. A 2013 OECD report predicted that full implementation would result in a 13 to over 15 per cent reduction of total trade costs.<sup>15</sup> This was confirmed by a more recent WTO

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<sup>14</sup>The article does allow the continuation of certain practices (specified in article 7:7:2).

<sup>15</sup>Trade Facilitation Indicators: The Potential Impact of Trade Facilitation on Developing Countries' Trade, OECD Trade Policy Working Paper, No. 144, 2013. The precise figures are 14.5% reduction of total trade costs for low income countries, 15.5% for lower middle income countries and 13.2% for upper middle income countries.

study<sup>16</sup> which showed that full implementation of the TFA can reduce Members' trade costs by an average of 14.3 per cent – greater than the trade cost reduction that would flow from the elimination of all remaining applied MFN tariffs. Both variable and fixed costs of exporting were predicted to fall. Over the 2015–30 horizon, implementation of the TFA could add up to 2.7 per cent a year to world export growth and more than half a per cent a year to world GDP growth.

Even larger reductions were anticipated with respect to import and export times. Full implementation of the TFA was projected to reduce time to import by over a day and a half (a 47 per cent reduction over the current average). Cuts in export time were even more dramatic – estimated to be shortened by almost two days (a 91 per cent reduction over the current average).

For time-sensitive goods – where the speed and predictability of delivery is critical – the report found that accelerated cross-border clearance under the FTA would provide an especially major boost to trade.

In addition to its own specific economic benefits, the TFA is also expected to give new impetus to deeper trade facilitation reforms globally. Indeed, it was already generating positive momentum in this direction even before the Agreement entered into force. In recent years, national and regional initiatives have increasingly been developed against the common TFA template and avoided piecemeal approaches that risked incompatibility and incoherence with corresponding reforms in other parts of the world. As economic interdependence deepens – and traders and investors increasingly seek harmonized rules and procedures – this informal 'coordinating' role of the TFA becomes especially significant.

In addition, the TFA offers a guarantee that the reforms it embodies are firmly locked in – giving traders and investors added assurances that the provisions of the new Agreement are permanent ones that cannot be altered by a change in administration. They can further rely on the provisions' enforceability. As WTO rules, the TFA articles are subject to the organization's dispute settlement mechanism, which substantially increases their chances of being effectively implemented and maintained 'on the ground'. The Agreement is further expected to create a culture of cooperation between government and business, and to secure political commitment for additional reforms.

## 6. What remains to be done?

With the adoption of the amendment protocol<sup>17</sup> (required to integrate the Trade Facilitation Agreement into the existing legal WTO framework), all decisions that

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<sup>16</sup>WTO World Trade Report 2015: Speeding up trade: benefits and challenges of implementing the WTO Trade Facilitation Agreement. All subsequently referenced findings are based on this report.

<sup>17</sup>The decision was taken by the WTO's General Council on 27 November 2014. See WT/L/940.

Table 1  
WTO Members which have already completed their TFA ratification process

WTO member	Date of deposit
Hong Kong, China	08.12.2014
Singapore	08.01.2015
United States of America	23.01.2015
Mauritius	05.03.2015
Malaysia	26.05.2015
Japan	01.06.2015
Australia	09.06.2015
Botswana	18.06.2015
Trinidad and Tobago	27.07.2015
Korea, Republic of	30.07.2015
Nicaragua	04.08.2015
Niger	06.08.2015
Chinese Taipei	17.08.2015
Belize	02.09.2015
Switzerland	02.09.2015
China	04.09.2015
Liechtenstein	18.09.2015
Lao People's Democratic Republic	29.09.2015
New Zealand	29.09.2015
Togo	01.10.2015
Austria	05.10.2015
Belgium	05.10.2015
Bulgaria	05.10.2015
Croatia	05.10.2015
Cyprus	05.10.2015
Czech Republic	05.10.2015
Denmark	05.10.2015
Estonia	05.10.2015
Finland	05.10.2015
France	05.10.2015
Germany	05.10.2015
Greece	05.10.2015
Hungary	05.10.2015
Ireland	05.10.2015
Italy	05.10.2015
Latvia	05.10.2015
Lithuania	05.10.2015
Luxembourg	05.10.2015
Malta	05.10.2015
Netherlands	05.10.2015
Poland	05.10.2015
Portugal	05.10.2015
Romania	05.10.2015
Slovak Republic	05.10.2015
Slovenia	05.10.2015
Spain	05.10.2015
Sweden	05.10.2015
Thailand	05.10.2015
United Kingdom	05.10.2015



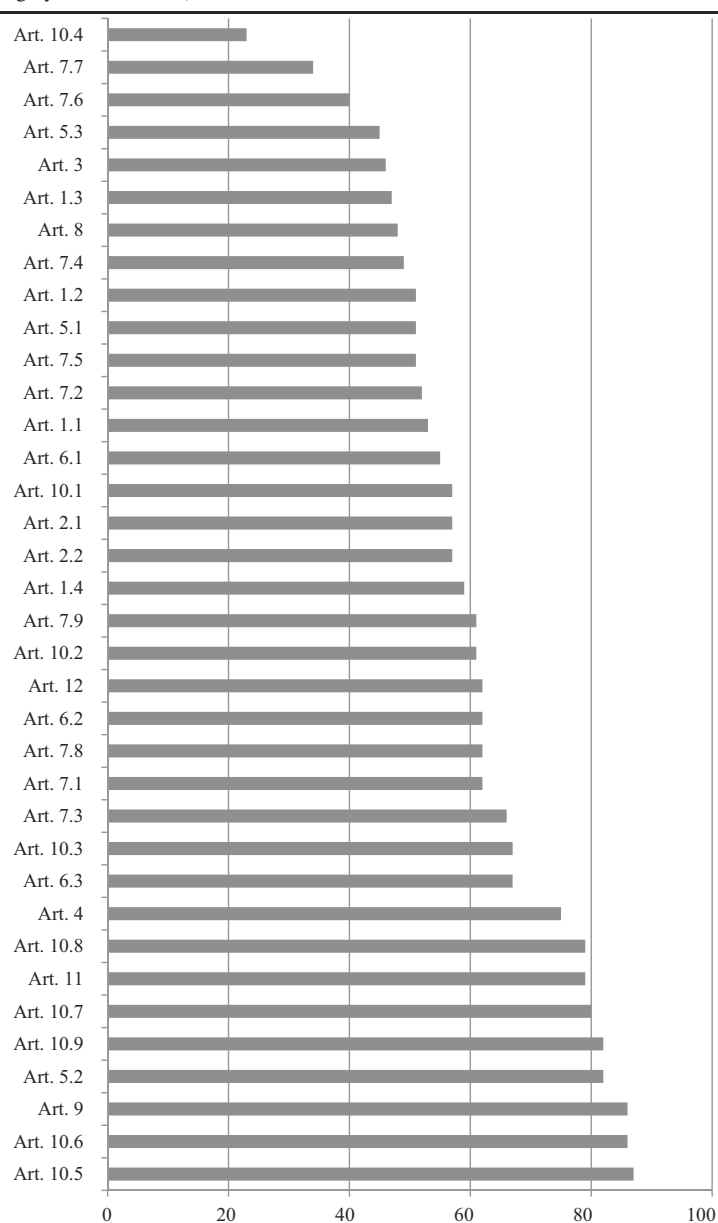
Table 1, continued

WTO member	Date of deposit
The former Yugoslav Republic of Macedonia	19.10.2015
Pakistan	27.10.2015
Panama	17.11.2015
Guyana	30.11.2015
Côte d'Ivoire	08.12.2015
Grenada	08.12.2015
Saint Lucia	08.12.2015
Kenya	10.12.2015
Brunei Darussalam	15.12.2015
Viet Nam	15.12.2015
Myanmar	16.12.2015
Norway	16.12.2015
Ukraine	16.12.2015
Zambia	16.12.2015
Georgia	04.01.2016
Lesotho	04.01.2016
Seychelles	11.01.2016
Jamaica	19.01.2016
Mali	20.01.2016
Cambodia	12.02.2016
Paraguay	01.03.2016
Turkey	16.03.2016
Brazil	29.03.2016
Macao, China	11.04.2016
United Arab Emirates	18.04.2016
Samoa	21.04.2016
India	22.04.2016
Russian Federation	22.04.2016
Albania	10.05.2016
Montenegro	10.05.2016
Kazakhstan	26.05.2016
Sri Lanka	31.05.2016
Saint Kitts and Nevis	17.06.2016
Madagascar	20.06.2016
Moldova, Republic of	24.06.2016
El Salvador	04.07.2016
Honduras	14.07.2016
Mexico	26.07.2016
Peru	27.07.2016
Saudi Arabia	28.07.2016
Afghanistan	29.07.2016
Senegal	24.08.2016
Uruguay	30.08.2016

required consensus by the entire membership were taken. This did not, however, mark the end of the road as it still left steps to be accomplished for the Agreement to enter into force.

At the 2013 Bali Conference, ministers had agreed on a specific ratification threshold for that to take place. By invoking article X:3 of the Marrakesh Agreement, it was

Table 2  
 Implementation priorities as expressed in category A notifications (percentage of overall category A notifications)



decided that two thirds of all WTO Members had to complete their respective domestic processes for the TFA to take effect. Work on ratification started immediately after the adoption of the amendment protocol, and acceptance instruments began to come in. As of 13 September 2016, their number had grown to 92, representing almost 85 per cent of what is needed for the Agreement to enter into force. More instruments are close to being submitted, creating reasonable hopes for the TFA to take effect soon.

Work on implementing the embodied reforms has already begun. Developed countries are getting ready to apply the entire Agreement as of day one. Developing and least-developed Members were allowed to design flexible implementation schedules. While equally obliged to implement the entire Agreement, they have the possibility to determine time frames and required capacity building support. The technical way of doing this is to group all measures into three categories:

- “A” containing provisions designated for implementation as of the day the Agreement enters into force,<sup>18</sup>
- “B” for provisions that require more time for their implementation and
- “C” for provisions whose implementation necessities both additional time and capacity building support.

Many such A, B and C notifications have already been submitted, especially with respect to category A. They give a good indication of when we can expect to see the TFA fully implemented, and which of its measures are considered to be a priority.

An analysis of how measures of particular interest to the pharmaceutical industry are classified reveals that most will be applied expeditiously (see Table 2).

Taken together, the state of the ratification and notification process to date paints a promising picture – and suggests that the Trade Facilitation Agreement is already starting to bring its many benefits to the business world.

### **Acknowledgements**

I would like to thank WTO Deputy Director General Xiaozhun Yi for having taken the time for a review. Suja Rishikesh-Mavroidis provided very useful comments and suggestions. Thanks are also due to María Alvarez de Cozar who prepared the input used for the second table.

### **References**

- [1] TN/TF/W/184, submitted on 5 December 2012.

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<sup>18</sup>Least-developed countries are given additional time to comply with all related category time-frames. For details, see articles 14 – 16 of the TFA.

- [2] Article 7:9 of the TFA, paragraph 1.
- [3] Article 7:9 of the TFA, paragraph 2.
- [4] Article 7:9 of the TFA, paragraph 4.
- [5] Neufeld Nora, Trade Facilitation under the Regional Trade Agreement Umbrella: Origins and Evolution, in: *Regional Trade Agreements and the Multilateral Trading System*, edited by Rohini Archaya, Cambridge University Press, 2016.

## The International Council for Harmonisation: Positioning for the future with its recent reform and over 25 years of harmonisation work

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The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, also known as “ICH”, is a key international harmonisation initiative founded by the drug regulatory authorities and industry associations from the European Union, Japan and the United States of America. The main objective of ICH is to promote public health globally through the development and implementation of harmonised guidelines and standards. With its recent reform, ICH became an Association under Swiss law, and set the stage to broaden its membership to regulatory authorities and international pharmaceutical industry associations beyond the three founding regions. Building on greater than 25 years of harmonisation work, ICH is now well-positioned to grow into a truly global venue for the development of guidelines and standards to facilitate the registration of human medicines across the world.

Keywords: Pharmaceutical, regulation, harmonisation, guidelines, standards

### 1. Introduction

Pharmaceutical drugs are an essential component of modern human medicine, and are developed for a variety of purposes ranging from diagnosis, prevention, treatment or the management of disease. Pharmaceuticals are developed to meet stringent regulations set by regulatory authorities in different countries, primarily to ensure that the public has access to medicines that are safe, effective and of high quality.

Over the past two decades, the pharmaceutical industry has become increasingly international, with research and development (R&D) shifting to emerging markets outside of Europe, Japan and the United States (U.S.), in search of better economies of scale [1,2]. The pharmaceutical industry aims to market its products as widely as possible, to provide broad access to medicines while optimizing the returns on

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investment. One of the advantages of globalization is capacity-building in emerging markets and greater access to high quality, safe, and effective medicines by different people across the globe. Greater returns on investment from globalization should lead to re-investment in research and innovation to continue work towards important future discoveries in human medicine.

Guidelines and standards are developed to help interpret the regulatory requirements and assist the pharmaceutical industry in meeting those requirements. Historically, different regulatory authorities have developed their own technical guidelines and standards, often resulting in divergent requirements across regions, which impact on the costs of R&D and delay access to new medicines. More recently, efforts by regulatory authorities and industry associations have emerged to work collaboratively to increase harmonisation of requirements and reduce duplication of efforts by industry when aiming to market their products in different countries. ICH is the main international initiative dedicated to developing harmonised guidelines and standards to facilitate the registration of human pharmaceuticals globally.

## **2. The origins of the International Council for Harmonisation (ICH)**

The harmonisation of regulatory requirements was pioneered by the European Community in the 1980s, as it moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonisation was feasible. At the same time, there were bilateral discussions between Europe, Japan and the U.S. on possibilities for harmonisation. It was, however, at the World Health Organisation (WHO) International Conference of Drug Regulatory Authorities (ICDRA) in Paris in 1989, that specific plans for action began to materialise. Soon afterwards, the authorities approached the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonisation, and ICH was conceived.

The ICH was launched in April 1990 at a meeting hosted by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in Brussels. ICH emerged as a tri-partite effort involving the European Community (now the European Union), the U.S. Food and Drug Administration (U.S. FDA), and the Japanese regulatory authorities (Ministry of Health, Labour and Welfare (MHLW), and the Pharmaceuticals and Medical Devices Agency of Japan (PMDA)) along with the industry associations representing these three regions, namely, EFPIA, the Pharmaceutical Research and Manufacturers of America (PhRMA), and the Japan Pharmaceutical Manufacturers Association (JPMA). At the first ICH Steering Committee meeting, it was decided that the topics selected for harmonisation would be divided into Safety, Quality, and Efficacy, to reflect the three criteria that form the basis for the regulatory authorisation of new medicinal products. ICH has since held bi-annual face-to-face meetings of its Steering Committee and various working groups working

on guidelines and standards, resulting in the publication of a myriad of harmonised guidelines for implementation across the participating regions and beyond.

Although ICH began as a tripartite effort, there have been several observers since its inception, including Health Canada, the WHO, and Swissmedic (previously representing the European Free Trade Association (EFTA)). Over the years, additional regulatory authorities and regional harmonisation initiatives have joined ICH as observers, making it a truly global venue for harmonisation work.

### 3. The objectives of ICH

The primary objective of ICH is to promote public health. The aim is to contribute to a more timely introduction of new medicines and continued availability of approved medicines to patients, by minimising the use of animal testing and preventing unnecessary duplication of clinical trials in humans, without compromising safety and effectiveness, as well as contributing to the development, registration and manufacturing of safe, effective and high quality medicines in an efficient and cost-effective manner.

ICH is a non-profit organization and does not pursue any commercial purposes. The work of ICH is accomplished through formal procedures and working groups involving the participation of experts nominated by the participating regulatory authorities and industry associations. The experts represent different perspectives, which combined, bring a wealth of knowledge and experience for the efficient development of guidelines and standards.

The work at ICH is complemented by other international regulatory harmonisation and collaboration initiatives such as the International Pharmaceutical Regulators Forum (IPRF), the International Generic Drug Regulators Programme (IGDRP), and the International Coalition of Medicines Regulatory Authorities (ICMRA). ICMRA in particular provides executive-level strategic leadership and direction for a range of areas that are common to many regulatory authorities' missions. These initiatives promote collaboration among regulatory authorities and provide an additional context for discussion of scientific issues that may either not be ready for work at ICH, or may be out of scope for ICH but nonetheless complementary for international harmonisation.

### 4. The recent reform of ICH

ICH was, until recently, known as the International *Conference* on Harmonisation. However, as of October 23, 2015, it became an Association under Swiss Law upon the finalization of the Articles of Association [3]. With this change, ICH became the International *Council* on Harmonisation, changed its governance structure (see Fig. 1) and funding model, and opened its doors to new members to widen the

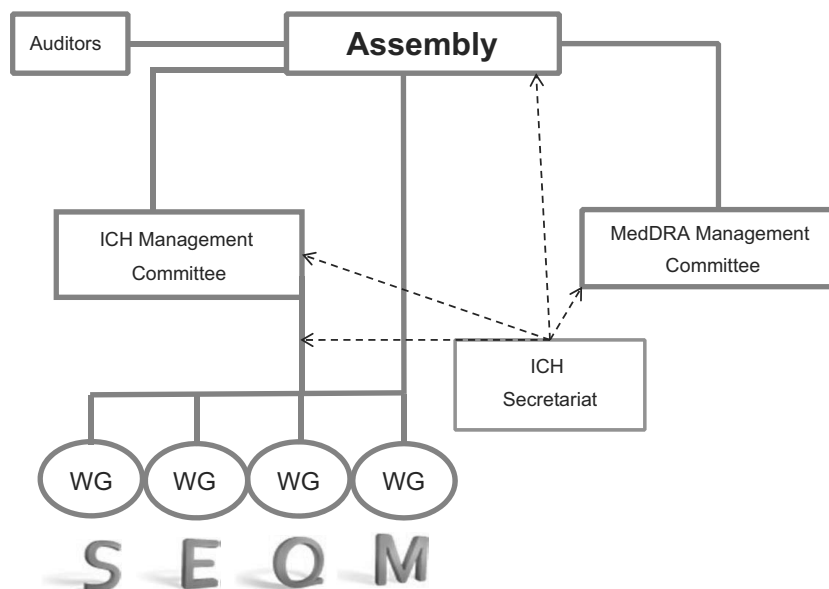


Fig. 1. Governance structure of the new ICH. WG = working group; S = Safety topic; E = Efficacy topic; Q = Quality topic; M = Multidisciplinary topic.

global reach of ICH. An important objective of the reform was also to increase the transparency of ICH activities.

Building on the 25 years of experience of the ICH Steering Committee, the new governance structure includes an Assembly and a Management Committee. The Assembly is the overarching body of the Association composed of all members (Table 1) and observers (Table 2) that takes decisions regarding governance aspects such as the Articles of Association, Rules of Procedure, admission of new members, adoption of new ICH topics, adoption of ICH guidelines, and setting membership fees. The U.S. FDA, European Commission and the Japanese MHLW and PMDA are the regulatory founding members of ICH, whereas the industry founding members are EFPIA, JPMA, and PhRMA. With the reform, Health Canada and Swissmedic were accepted as standing regulatory members of the ICH Assembly, in recognition of their contribution to ICH over the years. Furthermore, at the Assembly meeting held in Lisbon, Portugal, in June of 2016, two new industry members were accepted, specifically, the International Generic and Biosimilar Medicines Association (IGBA) and the World Self-Medication Industry (WSMI).

The Assembly uses a consensus-based approach for all decisions; however, if consensus is not reached on an issue, the decision is taken by a vote of the members, with each member having one vote.

The Management Committee is the body that oversees the operational aspects on behalf of all the members of the Association and has responsibility primarily for ad-



Table 1  
Current members of the ICH assembly and role in the management committee\*

Name	Membership status	Management committee role
European Commission (EC)	Founding Regulatory Member	Permanent Member
Ministry of Health, Labour and Welfare (MHLW) of Japan, also represented by the Pharmaceuticals and Medical Devices Agency (PMDA)	Founding Regulatory Member	Permanent Member
U.S. Food and Drug Administration (U.S. FDA)	Founding Regulatory Member	Permanent Member
European Federation of Pharmaceutical Industries and Associations (EFPIA)	Founding Industry Member	Permanent Member
Japan Pharmaceutical Manufacturers Association (JPMA)	Founding Industry Member	Permanent Member
Pharmaceutical Research and Manufacturers of America (PhRMA)	Founding Industry Member	Permanent Member
Swissmedic	Standing Regulatory Member	Permanent Member
Health Canada	Standing Regulatory Member	Permanent Member
International Generics and Biosimilar Medicines Association (IGBA)	Industry Member (as of June 2016)	Not currently participating
World Self-Medication Industry (WSMI)	Industry Member (as of June 2016)	Not currently participating

\*The new ICH Assembly and Management Committee were founded on October 23, 2015. Founding and Standing Regulatory Members, as well as Founding Industry Members, have been Permanent Members of the Management Committee as of the inauguration date of October 23, 2015. Each Permanent Member has appointed two representatives to the Management Committee. New members may be eligible in the future to nominate two representatives to the Management Committee, which may be appointed by election at the Assembly.

ministrative and financial matters. The reform introduced a funding model that relies less on industry-sourced funding. Under the previous ICH structure, the operations of ICH were supported by a Secretariat funded by ICH industry members and housed within the IFPMA. The funding of the venue for the bi-annual face-to-face meetings was primarily supported by the industry association of the hosting region. However, under the new ICH structure, the funding of ICH activities, including bi-annual face-to-face meetings of the ICH Assembly and the activities of the ICH Secretariat, are now provided by membership fees paid by its members.

The Management Committee is currently composed of two permanent representatives from each of the three founding regulatory members, the three founding industry members and the two standing regulatory members (Table 1), for a total of sixteen permanent representatives. IGBA and WSMI recently joined ICH, and may be eligible to nominate for election by the Assembly up to two representatives in the future, provided the party will meet the conditions defined by the Articles of Association (such as regular participation in all ICH meetings during the previous four years). In the future, it is expected that the Management Committee will have an

Table 2  
Current observers of ICH

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Southern African Development Community (SADC)
Gulf Cooperation Council (GCC)
Agência Nacional de Vigilância Sanitária (ANVISA, Brazil)
Pan American Network for Drug Regulatory Harmonization (PANDRH)
Asia-Pacific Economic Cooperation (APEC)
Association of Southeast Asian Nations (ASEAN)
Biotechnology Innovation Organisation (BIO)
Central Drugs Standard Control Organization (CDSCO, India)
Council for International Organizations of Medical Sciences (CIOMS)
Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico)
East African Community (EAC)
European Directorate for the Quality of Medicines & HealthCare (EDQM)
Health Sciences Authority (HSA, Singapore)
International Pharmaceutical Excipient Council (IPEC)
Ministry of Food and Drug Safety (MFDS, South Korea)
Rosdravnadzor (Russia)
Food and Drug Administration (TFDA, Chinese Taipei)
Therapeutic Goods Administration (TGA, Australia)
United States Pharmacopeia (USP)

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additional up to twelve elected representatives who will be elected from amongst the new regulatory and industry members expected to join ICH.

#### 4.1. Membership requirements for new members

The Articles of Association set out the requirements for entities interested in applying for membership at ICH. A pharmaceutical regulatory authority may be eligible to be a member if it has attended at least three ICH meetings during the previous two consecutive years, and has appointed experts in at least two working groups. The regulatory authority is also expected to have implemented the Q1: Stability Testing, Q7: Good Manufacturing Practice for Active Pharmaceutical Ingredients and E6: Good Clinical Practice guidelines in its jurisdiction.

New industry members are required to be a global pharmaceutical industry association representing a global constituency (i.e., with members from several countries in at least three continents). The industry association or its members must be regulated or affected by all or some ICH guidelines, have been an observer of the Association or interested party as defined prior to the establishment of the Association, and have appointed experts in at least two working groups.

#### 4.2. Rights and duties of regulatory and industry members

Regulatory members have the right to attend Assembly meetings and vote in the Assembly. While the founding regulatory members have a duty to appoint members in every working group, the standing and other regulatory members may appoint experts to working groups of their choosing. Regulatory members have exclusive

voting rights related to selection of new topics, and adoption, amendment or withdrawal of ICH guidelines. New regulatory members may wish to participate in the Management Committee, in which case, the regulatory member may propose two representatives for election by the Assembly, provided the party meets the conditions defined by the Articles of Association. All regulatory members are expected to implement ICH guidelines.

Industry members have the right to attend Assembly meetings and vote in the Assembly with the exception of decisions on selection of topics for ICH guidelines, and adoption, amendment or withdrawal of ICH guidelines. New industry members may propose two representatives for the Management Committee, for election by the Assembly, provided the party meets the conditions defined by the Articles of Association. Industry members may appoint experts to those working groups that are developing guidelines applicable to the industry member or its affiliates.

Industry members should actively support and encourage the compliance with the ICH guidelines applicable to the industry member or its affiliates. While the founding industry members are likely to appoint experts in every working group, the new industry members are expected to appoint experts in at least one working group that is developing an ICH guideline relevant to the industry member.

#### *4.3. Observers of ICH*

In recognition of the historical contribution of the WHO and the IFPMA, these organizations have been accepted as standing observers under the new ICH, in accordance with the Articles of Association. They may attend the Assembly and Management Committee meetings without any voting rights. They may also appoint experts to working groups.

Other entities have shown an interest in the work of ICH over the years, given the impact on international harmonisation. Under the previous ICH structure, the Global Cooperation Group was created in 1999 as a subcommittee of the ICH Steering Committee in order to make information available to any non-ICH party such as interested regulatory authorities, regional harmonisation initiatives, or pharmaceutical companies that requested the information. The non-ICH parties observed the open sessions of the old ICH Steering Committee, and many of these parties have now become official observers under the new ICH (Table 2), in accordance with the Articles of Association. The Articles of Association further define categories of observers, specifically, regulatory authorities, regional harmonisation initiatives, international pharmaceutical industry organizations and other international organizations with an interest in pharmaceuticals. Observers of the new ICH should have a contribution and benefit to ICH, and may attend the Assembly meetings without any voting rights.

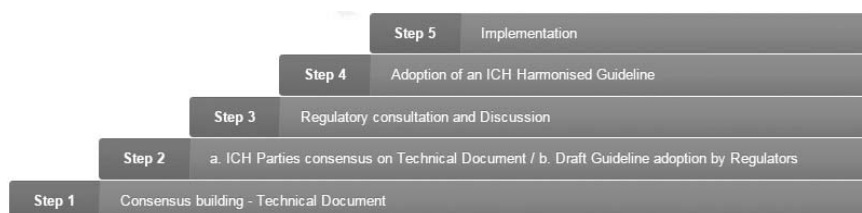


Fig. 2. Steps in the ICH guideline development process.

## 5. ICH guideline development process

Once a new topic is selected for harmonisation, and a concept paper and business plan are approved by the Assembly, an expert working group is formed to begin drafting the guideline. Each member of ICH appoints up to two experts to the working group. A rapporteur and a regulatory chair are chosen to help draft the technical document and guide the work in accordance with the concept paper and business plan. The expert working group works remotely via periodic teleconferences and meets face-to-face during the bi-annual ICH meetings, when necessary. The guideline-development process moves through a step-wise process as shown by Fig. 2.

The expert working group develops and maintains a workplan, including timelines for completion of each step of the work. Once Step 2b is reached (draft guideline is agreeable to the regulatory members of ICH), each regulatory member proceeds with Step 3 and carries out consultations in their region. The consultation period may range from 30 days up to 6 months, depending on the topic and regional consultation requirements. The timelines for reaching Step 5 (implementation) vary depending on the guideline and complexity of the topic, whether the output is a revised guideline versus a brand new guideline, or whether additional regulatory changes are required prior to implementation in a country or region.

Following the development of a guideline, an implementation working group may be organised to develop tools to facilitate the implementation of the guideline. Tools can include a Questions and Answers document, a slide deck, or other document as deemed necessary.

## 6. ICH achievements

ICH has delivered benefits to regulators and industry alike. Although industry benefits from harmonised global requirements that reduce duplication of efforts, regulatory authorities also benefit significantly from the exchange of knowledge, work-sharing, and the efficiencies gained with the ICH process. The guideline development process at ICH is based on science, driven by consensus, and is effectively managed to provide deliverables under strict timelines. In general, the ICH process requires

Table 3  
Summary of harmonised regulatory guidelines\*

Safety guidelines	
– S1A – S1C: Carcinogenicity studies	– S6: Biotechnology products
– S2: Genotoxicity studies	– S7A – S7B: Pharmacology studies
– S3A – S3B: Toxicokinetics and Pharmacokinetics	– S8: Immunotoxicology studies
– S4: Toxicity testing	– S9: Nonclinical evaluation for anticancer pharmaceuticals
– S5: Reproductive toxicology	– S10: Photosafety evaluation
Efficacy Guidelines	
– E1: Clinical safety for drugs used in long-term treatment	– E9: Statistical principles for clinical trials
– E2A – E2F: Pharmacovigilance	– E10: Choice of control group in clinical trials
– E3: Clinical study reports	– E11: Clinical trials in pediatric population
– E4: Dose-response studies	– E12: Clinical evaluation by therapeutic category
– E5: Ethnic factors	– E14: Clinical evaluation of QT
– E6: Good clinical practice	– E15: Definitions in pharmacogenetics/ pharmacogenomics
– E7: Clinical trials in geriatric population	– E16: Qualification of genomic biomarkers
– E8: General considerations for clinical trials	
Quality Guidelines	
– Q1A – Q1F: Stability	– Q7: Good manufacturing practice for active pharmaceutical ingredients
– Q2: Analytical validation	– Q8: Pharmaceutical development
– Q3A – Q3D: Impurities	– Q9: Quality risk management
– Q4 – Q4B: Pharmacopoeias	– Q10: Pharmaceutical quality system
– Q5A – Q5E: Quality of biotechnological products	– Q11: Development and manufacture of drug substances
– Q6A – Q6B: Specifications	
Multidisciplinary Guidelines	
– M1: MedDRA terminology	– M5: Data elements and standards for drug dictionaries
– M2: Electronic standards	– M6: Genotoxic impurities
– M3: Nonclinical safety studies	– M7: Electronic common technical document
– M4: Common technical document	

\*To download any of the ICH guidelines, visit the ICH website at [www.ich.org](http://www.ich.org). Information on accessing MedDRA is available on the ICH and MedDRA websites at [www.ich.org](http://www.ich.org) and [www.meddra.org](http://www.meddra.org).

a significantly lower level of resources from any one single regulatory authority to develop guidelines and standards compared to the resources required for regulatory authorities to carry out this work independently. Ultimately, however, harmonised requirements facilitate the development and registration of human medicines across the globe, which is intended to benefit patients the most.

Since 1990, over 60 guidelines and standards have been developed in a variety of topics and implemented across the regions participating in ICH. Table 3 lists the topics for which guidelines have been developed to-date. In particular, the Medical Dictionary for Regulatory Activities (MedDRA), the common technical document (CTD), and the electronic common technical document (eCTD) are important achievements.

MedDRA is a highly specific standardized dictionary of medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medicinal products both before and after a product has been authorized for sale. MedDRA

is currently available in 11 languages, and is open to anyone who would like to use it, with free access to all regulators, as well as to doctors and academics involved in non-commercial activities. A MedDRA Maintenance and Support Services Organisation (MSSO) serves as the repository, maintainer, developer and distributor of MedDRA. The activities of the MSSO are overseen by the MedDRA Management Committee. The costs of MedDRA are covered by subscription fees paid by pharmaceutical companies, with fees determined annually on a sliding scale linked to the annual turnover of companies.

The CTD is a standardized format for pharmaceutical companies to present the quality, safety, and efficacy information in the dossier of a new drug filed for review by the regulatory authorities. It was initially developed to facilitate paper filing, but it has evolved into an electronic format. The CTD/eCTD has revolutionized regulatory review processes by harmonising the format of drug submissions and enabling the implementation of good review practices. For industry, it has eliminated the need to reformat the information for submission to the different ICH regulatory authorities.

Several guidelines are currently under revision or development across the four streams of work products, specifically the efficacy, safety, quality, and multidisciplinary streams. Some of the new guidelines under development address topics such as pharmaceutical product lifecycle management (Q12), nonclinical safety testing of pediatric medicines (S11), and multi-regional clinical trials (E17). Revisions are also being undertaken for some guidelines that have not been updated for many years such as the S5: Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility, E6: Good Clinical Practice, E9: Statistical Principles for Clinical Trials and E11: Clinical Investigation of Medicinal Products in the Pediatric Population.

## **7. Stakeholder engagement**

An important aspect of the guideline development process at ICH is consultation with the affected stakeholders, spanning the regulatory, academic, and industry realms. ICH members and observers carry out consultation and engagement activities in their regions through presentations at regional conferences (e.g., Develop Innovate Advance (DIA) meetings)), or through consultations organized specifically for obtaining stakeholder input on specific ICH guidelines at Step 3. Consultations are crucial for gauging the feasibility of draft guidelines, seeking input from stakeholders beyond those that participate at ICH, and ensuring the final product will truly advance harmonisation efforts. By welcoming new members and observers, the ICH Association will continue to expand its engagement with a variety of stakeholders.

## **8. ICH into the future**

With its recent reform and 25 years of experience, ICH is indeed poised to grow into a truly global entity that facilitates the harmonisation of technical require-

ments for new and existing medicines. Transparency will remain at its core, with timely communication of information and engagement of stakeholders throughout the guideline and standard development process. ICH is also positioned to support training activities, to facilitate implementation and application of guidelines across multiple regions. ICH is developing a training strategy to promote the common understanding and interpretation of ICH guidelines. This should not only facilitate harmonisation, but also support worksharing among regions into the future, further increasing the efficiencies gained with harmonisation. The ICH website (<http://www.ich.org/home.html>) will be updated periodically to reflect the governance structure and activities of the new Association, including information on ongoing guideline development, meeting reports, the application process for Observership and Membership, and many other updates expected in the future.

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## **Towards African Medicines Regulatory Harmonization: The case of the East African Community**

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The role played by properly functioning regulatory systems towards enhancing access to essential medicines for patients is crucial. This is especially the case in Africa which has seen progressive growth in the regulatory environment. At the center of this growth has been the African Medicines Regulatory Harmonization (AMRH) initiative. This initiative seeks to strengthen regulatory capacity and encourage harmonization of regulatory requirements – with the ultimate aim of expanding access to quality, safe, and effective medicines for patients in need in Africa. A lot of progress has been made during the last years, with initial focus on the East African Community, where harmonization related regulations have already been implemented. The same is now being rolled out in other regions such as West Africa and the Southern African Development Community.

Removing bottlenecks and reducing redundancies in regulatory processes that slow access to medicines for patients in need today is critical. In this sense, collaboration between the World Health Organization and relevant stakeholders, including the research-based pharmaceutical industry, on collaborative registration procedures that support fast and efficient review and approval of essential medicines in Africa is essential.

African regulatory harmonization offers many benefits to regulatory authorities, patients in Africa and industry alike – and most critically for the protection of public health.

### **Background to the East African Community (EAC) Region**

Access to medicines remains a big challenge in the African continent including Anti-Retroviral Therapy coverage among people with advanced Human Immunodeficiency Virus (HIV) infection. Among the many factors that can be attributed to this current situation are the regulatory processes that are required to bring the medicines to patients [1]. The African medicines regulatory environment is as diverse as the number of countries on the continent. There has been general development in the regulatory landscape that is geared towards ensuring availability of safe and efficacious medicines to the populations that require them. With this general progression, often supported by partners such as the World Health Organization (WHO), among others, African countries have set up regulatory systems that are at different stages of maturity [2]. In between has been the realization among stakeholders that these regulatory systems have worked progressively to safeguard the public health of the population. However, they could also become, and have become, to a certain extent a hindrance to the timely access to medicines by the same population they are targeted to support [3]. In particular, diverse requirements developed by individual countries have

increased complexity and decreased the speed of access to the medicines without a commensurate increase in oversight due to the fragmented approach to medicines regulation. It is against this background, that the African Medicines Regulatory Harmonization (AMRH) initiative was launched by the East African Community (EAC) Medicines Regulatory Harmonization (MRH) on 30th March 2012.

The initiative was born out of the earlier pilot projects that had included the WHO joint assessment and WHO Prequalification (PQ) pilot projects of 2010 and 2013. The two WHO PQ pilots, dubbed WHO-EAC joint pilot assessment exercises, were led by WHO with participation of the EAC's national medicines regulatory authorities (NMRAs). In the case of the 2010 pilot, a record registration timeline of seven months was achieved by each of the NMRAs following the joint review exercise [1].

The EAC MRH was launched by the New Partnership for Africa's Development (NEPAD) Agency and the EAC, in collaboration with the AMRH partners WHO, Bill & Melinda Gates Foundation (BMGF), World Bank, the UK Department for International Development (DfID), and the Clinton Health Access Initiative [4]. It had been envisaged that the EAC MRH would be a key contributor towards access to quality, safe and efficacious medicines for priority diseases.

The program was anchored on the already existing EAC regional cooperation on health under Chapter 21 (Article 118) of EAC's treaty on health. The treaty provided for the harmonization of drug registration and regulation with a view of achieving good control of pharmaceutical standards without adversely affecting the movement of pharmaceutical products within the EAC [5]. In 2000, the EAC Council of Ministers, via the Research, Policy and Health Systems Working Group, tasked the EAC Secretariat to draft common drug policy and harmonized regulation and procedures. This policy culminated into the 2005 recommendation to promote regulatory harmonization through existing regional economic communities (RECs), including the EAC, by the African Drug Regulators Conference followed by the 2006 formation of five technical working groups (TWGs). on: administration, quality, good manufacturing practices (GMPs), safety and efficacy, and veterinary medicines. The five TWGs would remain dormant until 2009 when the respective NMRAs under EAC agreed to revitalize with WHO their commitment to support in the funding proposals that led to the launch of the EAC MRH [6,7].

Other partners, such as BMGF, DfID, German Technical Cooperation Agency (GTZ) and NEPAD agency joined WHO in confirming their interest to support the RECs' commitment to promote regulatory harmonization and the funding proposals in May 2009. The project was established with six goals including [5]:

1. Common technical documents (CTDs) for registration to be implemented by at least three EAC partner states;
2. An integrated information management system (IMS) established and linked in all the EAC partner states;
3. A platform for information sharing on harmonized medicines registration system to key stakeholders at national and regional level;

4. Regional and national capacity building to implement medicines registration harmonization;
5. A framework for mutual recognition of regulatory decisions made by other EAC partner states NMRAs; and
6. A quality management system (QMS) to be implemented in each EAC partner states.

In the end, the EAC MRH project was seen by stakeholders and partners to present benefits not only to the NMRAs, but also to the industry. The strengthening of the regulatory landscape in the EAC, as an outcome of the EAC MRH project, has been welcomed by the pharmaceutical industry as this is not only improving the availability of medicines, but also contributing to a well-defined and predictable system that is in line with international best practices such as the use of the CTDs format. Additionally, strengthening of the EAC's regulatory landscape is seen as an effort to increase the local capacity of the EAC's NMRAs and to bridge the gap between the various NMRAs. This capacity building in essence is seen to drastically reduce the learning curve especially among the less advanced NMRAs in the EAC. The lessons learnt from the EAC MRH initiative are crucial to scale up this model to other RECs, as is currently the case in Western Africa with the launch of the West African Health Organization (WAHO)-Economic Community of West African States (ECOWAS) harmonization initiative. Needless to say, the role of other partners, such as the WHO, has helped to ensure that regulatory harmonization is based on existing international best practices and procedures and thereby ensuring compatibility of the new harmonized processes and the NMRA processes with the global pharmaceutical industry practices. The EAC MRH initiative also aims to achieve the most optimal use of resources by encouraging and putting in place processes that facilitate regulatory information sharing, use of risk based approaches, as well as, joint activities. This optimal use of resources will progressively ensure that the already scarce resources at the EAC's NMRAs are put to the best and most value adding activities.

### **The journey to harmonized regulations**

The EAC MRH project was launched in response to the 2010 situational analysis developed by the NEPAD Agency [9]. The report aimed to establish the baseline of the regulatory systems in the EAC member states in view of the projected harmonization initiatives. It made reference to the EAC protocol, which is linked to the harmonization of medicines regulation in the EAC, and highlighted that the legislative regimes of the EAC member states lacked provisions for mutual recognition of regulatory decisions. It also showed that few EAC partner states had clear missions that linked directly to the EAC mission of establishing a common harmonized regulatory system in East Africa. This lack of direction was further exemplified by the fact that the EAC NMRAs were at different stages of achieving regulatory systems set up in the areas of medicines manufacture regulation and registration, distribution,

pharmacy practice and clinical trials regulation. Where registrations processes were in place, the guidelines differed in context, content and format. As regards the approval timelines, the report showed that registrations were taking up to 24 months with six months where fast track procedures were in place for priority disease areas (HIV, malaria and tuberculosis – TB). Regarding human resources, the report showed that there was a deficiency in the capacity and number of personnel working for the NMRAs. The report also demonstrated that the reductions in government funding (especially in those EAC member states where the NMRAs are domiciled within the ministry of health as medicines regulation departments) had a negative impact on the allocation of human resources. Additionally, the report indicated the presence of a pharmaceutical industry and industry associations at different stages of maturity with Kenya as the most developed in East Africa. According to the report, aspects of product registration system were considered to be non-value adding while others were omitted from the process. These redundant processes tended to introduce bottlenecks in the registration process leading to delays in the introduction of medicines in EAC's markets highlighting the need to simplify and standardize regulatory processes.

As a response the NEPAD agency, through the AMRH, started the EAC MRH as the first pilot via the 2011–2015 strategic plan. WHO provided technical support through a memorandum of understanding with the EAC to support the MRH. The project was launched in March 2012 marking the start of the implementation of the AMRH program.

Several partners played a pivotal role within the EAC MRH. In particular, many activities relied on the AMRH trust fund, financed by grants from the World Bank and BMGF among others. WHO was instrumental in helping to establish TWGs, which among other successes, achieved the creation of CTDs.

From early on, the activities amongst the EAC partner states were organized around the TWGs. This was driven by the fact that the EAC secretariat could only coordinate the activities while drawing the real technical input from the NMRAs. Secondly, it helped to begin to bridge the gap between the NMRAs as they began to work together not only to create the guidelines but also to diffuse their expertise across the EAC. This collaboration would in particular become an important aspect towards the mutual recognition stage later on.

The medicines evaluation and registration worked on harmonized registration guidelines structured around the CTD format while the EAC GMPs guidelines and manual were created by the GMPs TWG through a consultative process and under the guidance of the WHO's technical experts. The EAC's QMS requirements and guidelines for implementation of QMS manual were developed by the QMS TWG, while IMS implementation guideline and work plan were developed by the IMS TWG.

Specifically, the medicines registration TWG had the responsibility of developing harmonized technical requirements and guidelines for registration of human

medicines. Additionally, it was assigned to develop assessment guidelines and standard operating procedures for assessment of medicines dossiers and finally identify and develop a list of vital essential and necessary medicines that was to be jointly assessed by the EAC partner states for approval to the steering committee.

During the development of the various working documents and guidelines, the respective NMRAs shared work via face to face meetings and joint working sessions. As an effort to diffuse the knowledge among personnel from the EAC's NMRAs, Zanzibar, Rwanda and Burundi received support to come closer to the level of advancement of Kenya, Uganda and Tanzania. As an outcome, this collaboration between the EAC member states not only contributed to increase the trust among each other, but also to transfer knowhow among NMRAs personnel.

Ultimately, the draft guidelines were reviewed publically by stakeholders including the pharmaceutical industry (both locally and globally) through the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) between 2013 and 2014. This consultation culminated in the endorsement of the guidelines compendium by the EAC Council of Ministers in September 2014 [10]. In January 2015, the EAC Secretariat issued for the first time a call for expression of interest (EOI) to industry for application of new drug application through the EAC Joint Assessment Program [11]. This EOI was limited to priority products for mother and children, medicines for neglected diseases, anti-cancer medicines, and antimalarial, anti-retroviral and anti-TB medicines. Industry responded with several applications which were evaluated jointly with support from WHO and Swissmedic resulting in the recommendation of the first two products for licensing by the EAC partner states. In parallel, the EAC member states started the national harmonization of the medicines registration guidelines: Kenya (July 2015), Tanzania (July 2015), Rwanda (December 2014), Burundi (September 2015), Zanzibar (June 2015), and Uganda (July 2014).

The EAC secretariat established a process for receiving and processing applications as detailed in Fig. 1. The submission is performed to the lead country, Tanzania, followed with screening of the applications within a period of two weeks. This is to be followed by dossiers scheduling on a first come first out basis. The review time is scheduled at 90 days and is provided to have full or abridged evaluation. Upon completion of evaluation the applicant receive registration approval from the respective NMRAs within 90 days. Deficiency Letters responses are allowed for a 60-day period.

Since the launch of the EAC MRH process, a total of 21 products have been submitted. Sixteen out of these 21 products have been evaluated resulting in four registration recommendations out of the first group of eight products, while another set of eight products began the evaluation process in May 2016 with five products currently at the screening stage [12]. Since then, EAC secretariat has issued a second call for EOI which contains an expanded list of eligible products including reproductive health products [13]. It is expected that the success of the first call for EOI will be replicated in this phase.

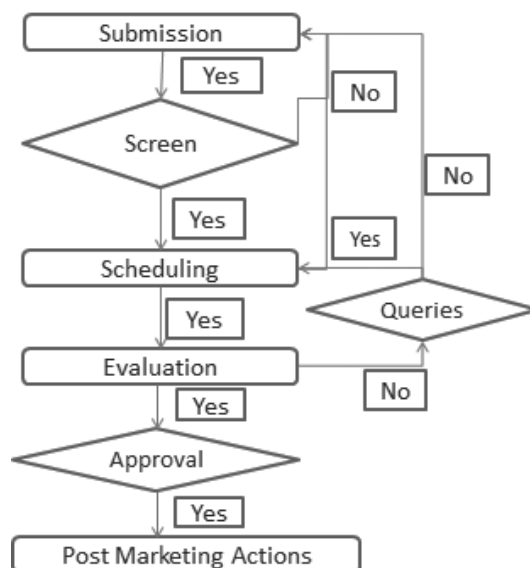


Fig. 1. Submission, evaluation and post marketing process flow for the EAC MRH. Source: EAC Secretariat (<http://www.eac.int/>).

Additionally, one of the challenges identified by the 2010 NEPAD report referred to a lack of legislation that supports the establishment of regulatory bodies among EAC member states. Since then, the NEPAD Agency, through the AMRH mandate, has led the efforts to develop a model law that guides member states' NMRAs with a base line non-prescriptive law. This law, which was approved by the African Union (AU) Specialized Technical Committee on Justice and Legal Affairs in November 2015, is open for use as a basis for establishing regulatory bodies and supporting legislation in AU member states [14,15]. This model law is expected to provide EAC countries with support in further developing national legislation as necessary.

### Role of the pharmaceutical industry in the EAC MRH

The pharmaceutical industry has been a key player and contributor to the development of the EAC MRH through the provision of technical input during the guidelines' production, publication and implementation [16]. The creation of harmonized regulatory guidelines in the EAC has reduced medicines' approval timelines and, as a consequence, decreased the waste of resources (e.g. application of abridged reviews) [12,17] increasing the attractiveness of the African region to the pharmaceutical industry for the introduction of new products with the potential of simultaneous launch. As a result, access to safe, effective and high quality medicines for the treatment of priority diseases has been enhanced.

It is foreseen and expected that the EAC MRH will be extended to develop a framework of mutual recognition of past regulatory decisions by the EAC's member states and achieve full integration of the EAC as a regional health authority. This integration will require a transition from the current joint assessment approach to centralized applications and finally to mutual recognition status [18]. The 2010 NEPAD report stressed that the EAC would continue to act as the benchmark for the rest of the African RECs as Africa works towards the establishment of one regulatory body (i.e. the African Medicines Agency). It is expected that this successful working system will be extended to other regulatory activities such as post market surveillance and variations [19]. As the current guidelines for medicines registration only covers small molecule products, other guidelines will have to be developed to cover biotherapeutic medicines and vaccines.

The handling of GMP certifications should adopt a risk-based approach across the region beyond the current joint inspection approach. This will require the use of desk reviews, recognition of other regulatory bodies' inspection reports, and risk categorization of manufacturing activities. The adoption of the model law should be fast tracked by countries that lack adequate legislation frameworks to establish properly functioning regulatory bodies [2]. In particular, the establishment of the food and drug authority model (as in the United States and Taiwan), distinct and anonymous from the national ministries of health in the EAC member states and with clear funding structures from the national governments, should be effected across the partner states in addition to the establishment of a centralized body at the EAC Secretariat. The financial sustainability of the EAC MRH remains unguaranteed and there is a need to secure it through both national and regional initiatives. The transition clauses need to be defined and anticipated. For instance, the recent announcement of South Sudan joining the EAC economic zone would require forward looking guidance on how the new country will adopt the already evaluated and approved products through the joint assessments prior to South Sudan joining the EAC. It is imperative that the administrative hurdles that characterize the national systems are eliminated from the EAC procedure especially as more applicants come on board.

## **Conclusion**

The EAC MRH has come a long way from its initial pilot projects. This has taken the efforts of all stakeholders including the pharmaceutical industry and the EAC member states to achieve the current success. It is important to note that despite the challenges that plague the region, the above successes have been accomplished in a relatively short time period. The region should not slow down on this momentum as this approach has demonstrated its potential to significantly increase access to quality and efficacious medicines and, at the same time, positions the EAC region as an attractive region for the pharmaceutical industry to establish their presence. This has

also demonstrated that with adequate coordination and sharing of information as dictated by global trends, it is possible to shorten the learning curve even with regulation of medicines. This implies that the scaling and transfer of these successes to the rest of Africa, namely WAHO and Southern African Development Community (SADC) regions, remains a promising endeavor. EAC should now move to the next stages of lifecycle management regulatory framework (e.g. variations), and regulation of biotherapeutic medicines among others. Establishment of a regional pharmaceutical policy and regulatory framework remains a priority goal of the EAC.

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## **Accelerating patient access to medicines in the Economic Community of West African States, the Southern African Development Community and the organization for the coordination of the fight against endemic diseases**

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The role played by properly functioning regulatory systems towards enhancing access to essential medicines for patients is crucial. This is especially the case in Africa which has seen progressive growth in the regulatory environment. At the center of this growth has been the African Medicines Regulatory Harmonization (AMRH) initiative. This initiative seeks to strengthen regulatory capacity and encourage harmonization of regulatory requirements – with the ultimate aim of expanding access to quality, safe, and effective medicines for patients in need in Africa. A lot of progress has been made during the last years, with initial focus on the East African Community, where harmonization related regulations have already been implemented. The same is now being rolled out in other regions such as West Africa and the Southern African Development Community.

Removing bottlenecks and reducing redundancies in regulatory processes that slow access to medicines for patients in need today is critical. In this sense, collaboration between the World Health Organization and relevant stakeholders, including the research-based pharmaceutical industry, on collaborative registration procedures that support fast and efficient review and approval of essential medicines in Africa is essential.

African regulatory harmonization offers many benefits to regulatory authorities, patients in Africa and industry alike – and most critically for the protection of public health.

Keywords: AMRH strategic plan; Africa Medicines Regulatory HARMONIZATION; Economic Community of West African States (ECOWAS) and the ECOWAS Regional Pharmaceutical Plan; Southern African Development Community (SADC); Organization coordinating endemic diseases in Central Africa (OCEAC); Regional Economic Communities (REC); Agreements for Mutual Recognition; National Medicines of Regulatory Authorities (NMRA); GMP inspection; Africa Medicines Agency (AMA); New Partnership of Africa Development (NEPAD)

### **1. Introduction**

The African continent has undergone various alignments and changes over the last five decades. Among these developments have been the establishment of regional economic blocks, also known as Regional Economic Communities (RECs). The RECs were formed independently, and are comprised of geographical groupings of African countries as a means of promoting the integration of common regional

interests and processes. Among the key areas of recent collaboration and alliance within each block there has been a common goal of improving the healthcare sector within their respective regions. These developments are not only important to each region, but also to all Africa as well, since the RECs provide an opportunity for collaboration across the African Union's (AU).<sup>1</sup>

In this regard, it should be noted that the AU, through its technical arm, the New Partnership for Africa's Development (NEPAD) Agency,<sup>2</sup> has established a medicines regulatory harmonization initiative with the ultimate aim of establishing one central regulatory body in Africa, the African Medicines Agency (AMA). This initiative dubbed the African Medicines Regulatory Harmonization (AMRH) Programme<sup>3</sup> has established a roadmap towards realizing this goal through the intermediate steps being taken by the various RECs.

The World Health Organization (WHO) is also playing a strong role in the AMRH Programme by providing technical assistance in the development and implementation of harmonized processes via supporting technical working groups within the AU. Four technical working groups were officially constituted in 2012 where a respective African member state national medicines regulatory authority (NMRA) took the technical lead in the development of regional guidelines, with the support of another member state NMRA. These working groups focus on the utilization of a common technical document (CTD); along with shared good manufacturing practices (GMPs); information management systems (IMSs); and quality management systems (QMSs) [1].

This article will look at three African RECs – the Economic Community of West African States (ECOWAS), the Southern African Development Community (SADC) and the Organization de Coordination pour la Lutte Contre les Endémies en Afrique Centrale (OCEAC) – and discuss how they are working closely with their respective member states' NMRAs in developing regional medicines registration harmonization proposals to increase patients' access to quality, safe and efficacious medicines. In addition, this article will also discuss how these developments, many of which are complementary, can facilitate the AMRH Programme moving forward.

The AMRH's initiatives are also further described, along with the AMRH's progressive implementation efforts in these regional economic communities [1].

## **2. Economic Community of West African States (ECOWAS)**

The ECOWAS is the regional economic organization for West Africa, headquartered in Abuja, Nigeria. It is composed by the following countries: Benin, Burkina

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<sup>1</sup>African Union (AU) <http://www.au.int>.

<sup>2</sup>New Partnership for Africa's Development (NEPAD) Agency [www.nepad.org](http://www.nepad.org).

<sup>3</sup>African Medicines Regulatory Harmonization (AMRH) Programme <http://www.nepad.org/content/african-medicines-regulatory-harmonisation-armh-programs>.

Faso, Cape Verde, Ivory Coast, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone and Togo. The ECOWAS was founded with the mandate of promoting economic integration in all fields of activity within its constituting countries. However, the diversity of culture and languages (French, English and Lusophone) within the region have in general presented challenges in the past, resulting in disparate medicines registration processes and patient access within this region. Therefore, the current main objective of the ECOWAS is to overcome these hurdles through greater cooperation within the region to enhance the convergence of regulatory requirements.

In 2014, the West African Health Organization (WAHO) (WHO's regional agency in West Africa) developed the ECOWAS Regional Pharmaceutical Plan (ERPP) [2]. The ERPP provides a clear roadmap to support the harmonization of robust medicines regulatory systems in the ECOWAS. The ERPP's vision is to improve the quality control of laboratories and centers of excellence for the local production of medicines and the support of local clinical trials, as well as, strengthening the medicines regulatory harmonization processes, while recognizing the need for enhanced collaborations with global stakeholders to facilitate the production and distribution of high quality standard medicines. The full implementation of the ERPP objectives will take some time since they involve overcoming local manufacturing challenges, establishing robust regulatory systems, creating centers of excellence for quality control laboratories, and generating an ecosystem which enables pharmaceutical sector growth. Hence, the ERPP objectives have been defined as a long term vision up to the year 2025.

As a first step, the ECOWAS is focusing on the quality control of regional laboratories and centers of excellence for the local production of medicines. In 2015, the ECOWAS launched the AU's AMRH Programme focusing on the development of national and regional roadmaps for GMPs. Some regional accreditation initiatives are also planned to strengthen the regional GMPs and to help further shape the regulatory harmonization efforts in Africa.

This effort is intended to build upon various pharmaceutical supply programs previously initiated in the region by WAHO. Since 2010, WAHO has initiated several programs to strengthen the capacity of quality control (QC) laboratories in selected ECOWAS' countries [2]. Among these WAHO programs are: the development of guidelines and training manuals for laboratory quality management systems; the training of laboratory managers and staff in the utilization of these manuals and guidelines; and the selection of five QC laboratories to upgrade and support attainment of ISO 17025 certification and the subsequent elevation to the status of centers of excellence for the testing of medicines. Despite WAHO's efforts, only two countries (Nigeria and Ghana) have been qualified as laboratories of control in alignment with ISO standards. Thus, more work on WAHO's programs to strengthen the capacity of QC laboratories is envisioned to be implemented/take place.

Over the past five years, a number of programs have been initiated by the WAHO in collaboration with the ECOWAS to strengthen the manufacturing capacity of selected pharmaceutical firms and the supply of anti-malarial and anti-retroviral drugs

within the region [2]. To foster the ECOWAS's commitment towards improving the local pharmaceutical production of medicines, the 14<sup>th</sup> African Assembly of Health Ministers endorsed the "ECOWAS Charter on Public Private Partnership Initiative for Local Pharmaceutical Production of Priority Essential Medicines" in Praia, Cape Verde in April 2013. The WAHO has also supported the development of the guidelines for the ECOWAS/WAHO's Certification Scheme for Finished Products, Raw Pharmaceutical Materials and Pre-qualification Requirements for the evaluation of pharmaceutical manufacturers for market authorization.

In addition, within the ECOWAS region, the CTD format has been developed for the registration of medicines, pharmacovigilance, and inspections among other specific and technical fields. The harmonization of local regulations, in alignment with the regional ones, will facilitate joint review and mutual recognition of the regulatory activities (e.g. medicines registration and approval) conducted by the different NMRAs within the ECOWAS region. These efforts were facilitated by earlier work performed by the West African Economic and Monetary Union (WAEMU), also known by its French acronym, UEMOA. The WAEMU had worked beforehand with eight Francophone countries within Africa on a CTD format. Following the 2014 resolution, backed by the WHO to consolidate harmonization activities under the WAHO within the region, the WAEMU and its past CTD efforts helped to finalize a region-wide CTD format which was approved at the ECOWAS Ministers of Health Meeting in April 2016.

In the last five years significant improvement in several regulatory affairs and quality activities have been achieved within the ECOWAS REC in alignment with the AMRH Programme goals. Looking ahead, the WAHO, in collaboration with its regional member states and partners, is in the process of organizing the 2<sup>nd</sup> ECOWAS Good Practices Forum in Health in October 2016 in Ivory Coast. This Forum will serve as a platform to further identify key strategic issues on good practices, and innovative approaches to develop future recommendations and resolutions to the ministers of health of the ECOWAS REC.

### **3. Southern African Development Community (SADC)**

The SADC is a REC comprising 15 member states: Angola, Botswana, Democratic Republic of Congo, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Swaziland, Tanzania, Zambia and Zimbabwe. Established in 1992, the SADC is committed to regional integration and poverty eradication within Southern Africa through economic development and ensuring peace and security.

During the SADC Health and HIV and AIDs Ministers joint meeting held in November 2013 an agreement was reached to review and update the SADC regional registration guidelines to streamline them with internationally recognized standards (e.g., the International Council for Harmonization of Technical Requirements for

Pharmaceuticals for Human Use – ICH, or WHO, among others) for the registration of medicines, and the use of a CTD format within the region [3]. The updated version of the SADC regional registration guidelines, along with the CTD format were approved by the SADC Ministers in January 2015 [4]. Since then, member states have adopted the SADC regional registration guidelines at the diverse national level. The adoption of a CTD format and regional registration requirements facilitate submit applications for the registration of medicines in a common single format within the SADC region, and enhances cooperation between the SADC's NMRAs. Moreover, regulators in the SADC region, through the ZAZIBONA Initiative, have been collaborating together towards better medicines registration processes to improve access to quality medicines.

Updating and harmonizing regulatory standards to create one regional market and facilitate mutual recognition is just one part of the draft Strategy on Regional Manufacturing of Essential Medicines and Health Commodities (2016–2020), which supports the pharmaceutical component in the SADC's Industrialization Strategy and Roadmap 2015–2063 [5]. A harmonized regulatory process, including a harmonized GMP certification, is essential for facilitating the approval of new products, and increasing the market uptake for locally produced products.

Despite the work done to date, the SADC's NMRAs recognize the continued challenges the pharmaceutical industry faces with respect to the varying regulatory requirements within the region [6]. While the regional registration guidelines have been updated and a harmonized SADC CTD format approved, common product information, labelling format and harmonized GMPs requirements are lacking.

To this end, the SADC, in partnership with the NEPAD, the WHO and the World Bank, organized a workshop in April 2016 for regulators and representatives of the pharmaceutical industry to discuss the harmonization of medicines registration and GMPs certification within the region. The work is in line with the approved SADC Pharmaceutical Business Plan 2015–2019 [7], the SADC Industrialization Strategy (2015–2063) [4] and the draft Strategy on Regional Manufacturing of Essential Medicines and Health Commodities (2016–2020) [3]. The objective of the SADC workshop, held in South Africa in April 2016, was to review the AMRH progress achieved on the regulatory convergence initiatives regarding labelling and GMP requirements, along with further actions needed, and the status of the implementation of the approved SADC registration guidelines and CTD format, and GMP standards by SADC member states.

Common GMP standards are considered essential within the region to ensure the protection and promotion of public health, production of medicines and health commodities. While the WHO GMPs guidelines are generally used or referred to as the standard within the SADC region, there is a non-uniform application of these standards across the region leading to the existence of diverse GMPs guidelines across the SADC region. Further, with respect to international recognition of quality assurance mechanisms used within Africa, at this time, South Africa's Medicines Control Council (MCC) is the only African NMRA that has been granted membership in the

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/s).<sup>4</sup>

To help address differences in the application of GMPs within the regions, along with other observed divergences in regulatory practices, the SADC has identified the following key strategic priorities to be addressed in 2016–2019 [6]:

1. Create an environment that will maximize the research into production capacity of local and regional pharmaceutical industry in terms of generic essential medicines;
2. Strengthen regulatory capacity by assessing NMRAs to identify critical areas of weaknesses in control and registration;
3. Develop strategies to strengthen selected NMRAs;
4. Utilise the harmonised SADC medicine regulation guidelines; and
5. Set up of technical working group to facilitate the implementation of the roadmap was agreed as a next step.

#### **4. Organization for the Coordination of the Fight against Endemic Diseases (OCEAC)**

The OCEAC is a regional Economic community comprising the following countries: Cameroun, Congo, Gabon, Equatorial Guinea, Chad, and Republic Central Africa.

In its beginnings (between 1965 and 1983) the OCEAC was responsible for: 1) setting and coordinating all programs of action for the control and eradication of major endemic epidemics in the Central African Region (e.g. tuberculosis, malaria, intestinal parasites), and 2) following up studies and conducting research to succeed in the fight against endemic epidemics.

The involvement of OCEAC in the AMRH Programme began in July 2015. NEPAD is coordinating the AMRH Programme within the region and has empathized the on-going collaboration between the OCEAC and WHO.

At the AMRH 5<sup>th</sup> Advisory Committee Meeting held in Dakar in May 2016, Dr. Aime Djitafo Fah, Coordinator of the OCEAC's Regional Sub-Program Harmonization of National Pharmaceutical Policies in Central Africa, introduced the OCEAC's governance structure and a brief background report on the progress made in the medicines regulatory harmonization field (e.g. the development of registration guidelines) in this region since 2006. During his presentation, Dr. Aime Djitafo

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<sup>4</sup>PIC/S is an international collaboration initiative, comprised of 48 participating authorities across the globe. PIC/S membership is dependent upon the demonstration of GMP inspection systems comparable to that of the PIC/S. PIC/S mission is *to lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products*", which can facilitate mutual recognition of inspections amongst members. [www.picscheme.org](http://www.picscheme.org).

Fah highlighted the importance to continue the advocacy and coordination efforts towards the implementation of the AMRH Programme in Central Africa; and reiterated OCEAC's willingness to continue collaborating with ECCAS. During the AMRH 5<sup>th</sup> Advisory Committee Meeting, it was also discussed the implementation plan for the period 2014–2018 which focuses on the following priority areas [8]:

1. Conduct joint training on guidelines;
2. Establish regional ethics committee to facilitate local clinical trials;
3. Establish a Regional Commission on pharmacovigilance; and
4. Draft legislation to assist combating counterfeit medicines.

There are significant ongoing efforts on cooperation between the Economic Community of Central African States (ECCAS) and the OCEAC on the implementation of the AMRH Programme in the Central African region. The collaboration framework and roadmap for the AMRH roll out in the Central Africa region will be signed in 2016 by NEPAD Agency, WHO, and OCEAC.

High level discussions regarding the implementation of the AMRH Programme in the Central African region were held in 2015 during the 4<sup>th</sup> AMRH Advisory Committee Meeting under the leadership of the *Economic Community of Central African States* (ECCAS) and OCEAC.

Other efforts underway include the Harmonization of National Pharmaceutical Policies in Central Africa to help align the current different regulations and practices governing pharmacies in order to opt for an identical and common policy in the countries of the Central African sub-region.

In recognition of the existing efforts to advance the pharmaceutical sector in the Central African region, the AMRH Programme undertook to engage ECCAS and OCEAC with a view to develop a framework and a roadmap for the implementation of AMRH in the Central African Region [8].

## **5. Common topics to the three RECs**

### *5.1. GMP standards and GMP inspections*

A common theme within the ECOWAS, SADC and OCEAC is the need to harmonize quality standards and cooperative agreements for the mutual recognition of member states' GMP inspections and master batch records (MBRs). Currently, GMP inspections and MBRs have not been implemented harmoniously leading to remarkable regulatory discrepancies between the different NMRAs in these RECs.

During the last AMRH Advisory Committee held in May 2016 in Dakar one of the key topics discussed was the implementation of GMPs Roadmaps through the AU Pharmaceutical Manufacturing Plan for Africa (PMPA) [8]. The overall goal of this meeting was to develop regional GMP approaches to reach alignment and harmonization of national GMP roadmaps within the PMPA and AMRH Frameworks. The

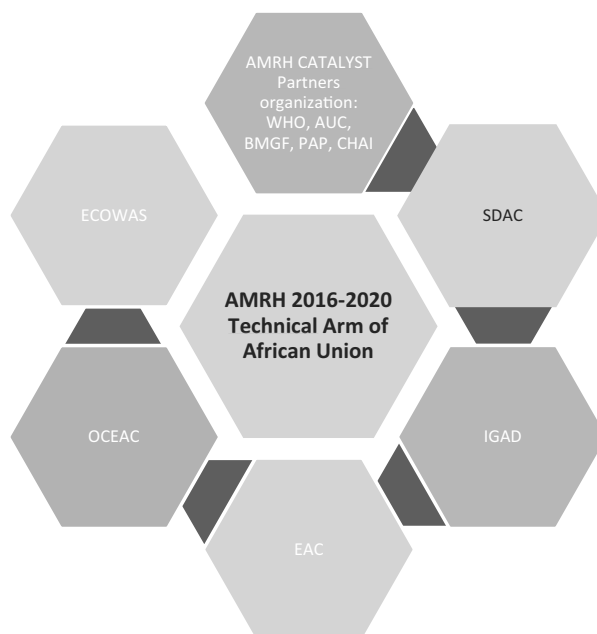


Fig. 1. Africa networking platform.

core objectives of the GMPs roadmap are to identify existing regional GMPs certification schemes, and support RECs to develop strategies and approaches to achieve universal GMP standards by the local pharmaceutical manufacturers in Africa.

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) position paper *GMP Inspections and the Provision of Batch Records in Sub-Saharan Africa* stresses that GMPs inspections are a fundamental path that NMRAs can use to ensure the production of high quality pharmaceutical products [9]. Recognizing stringent regulatory authorities (SRAs) and the mutual recognition of African NMRA inspections and implementation of the above mentioned practices may be a more resource efficient way of providing assurance with GMP compliance. A positive inspection report or a valid GMP certificate from an SRA can negate the need for a duplicative inspection.

### 5.2. AMRH strategic direction

As background, the origin of the AMRH Initiative goes back to 2007 with the assembly of a consortium of key partners (the United Kingdom's Department for International Development or DFID, Bill & Melinda Gates Foundation, NEPAD, Clinton Foundation, and WHO) established to accelerate and ensure medicines regulatory harmonization in Africa. The AMRH Initiative led to the creation of the



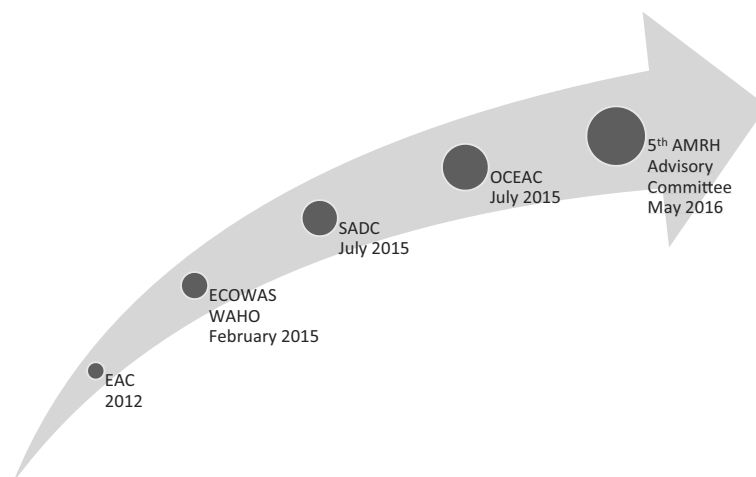


Fig. 2. Chronological overview of the AMRH implementation.

AMRH Programme in 2010 through which the NEPAD, as the technical arm of the AU, in collaboration with partnering stakeholders, is supporting African RECs efforts towards regulatory harmonization and increase African patients access to essential medicines. Drawing upon the past experiences around the globe, the Africa Union, its RECs and partnering organizations involved in the African Networking Platform (see Fig. 1) are leveraging lessons learnt from other harmonization models and schemes within ICH, Europe, America and Asia to help Africa to achieve an efficient harmonization process.

The new AMRH Programme Strategic Plan for 2016–2020 will build upon past efforts (see Fig. 2) and is intended to provide continued support to the NEPAD and its collaborating partners to ensure the implementation of the AMRH Programme over the next five years.

IFPMA, through its African Regulatory Network (ARN) activities, supports the implementation of the AMRH Programme by sharing IFPMA member companies' extensive and global technical expertise in pharmaceutical development and manufacturing. Ongoing communication amongst all stakeholders is essential, and the African Regulatory Conference, supported by the ARN, provides a platform to bring NMRAs, the biopharmaceutical industry, and other stakeholders together to share, collaborate and establish clear milestones towards regulatory harmonization in Africa to improve patients' access to quality drugs.

## 6. Conclusion

The individual activities conducted by the ECOWAS, SADC and OCEAC are intended to help collectively to lay the ground work for the implementation of the

AMRH Programme over the next five years. The envisioned benefits of the AMRH Programme include: increased patient access to quality medicines; optimized labelling requirements that enable packaging sharing across member states, thus facilitating the distribution and supply of needed medicines across the continent; and harmonized GMP standards for sharing GMP Certificates provided to regulators to reduce duplicative inspections. In parallel, to support the AMRH Programme, the AU, WHO, and NEPAD are collaborating to ensure the endorsement of the establishment of the AMA by the Summit of AU Heads of State and Government in 2018.

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## Accelerating regulatory approvals through the World Health Organization collaborative registration procedures

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Towards African Regulatory harmonization processes – Accelerating patient access to medicines.

The role played by properly functioning regulatory systems towards enhancing access to essential medicines for patients is crucial. This is especially the case in Africa which has seen progressive growth in the regulatory environment. At the center of this growth has been the African Medicines Regulatory Harmonization (AMRH) initiative. This initiative seeks to strengthen regulatory capacity and encourage harmonization of regulatory requirements – with the ultimate aim of expanding access to quality, safe, and effective medicines for patients in need in Africa. A lot of progress has been made during the last years, with initial focus on the East African Community, where harmonization related regulations have already been implemented. The same is now being rolled out in other regions such as West Africa and the Southern African Development Community.

Removing bottlenecks and reducing redundancies in regulatory processes that slow access to medicines for patients in need today is critical. In this sense, collaboration between the World Health Organization and relevant stakeholders, including the research-based pharmaceutical industry, on collaborative registration procedures that support fast and efficient review and approval of essential medicines in Africa is essential.

African regulatory harmonization offers many benefits to regulatory authorities, patients in Africa and industry alike – and most critically for the protection of public health.

Keywords: Accelerated registration, collaborative registration procedure, joint reviews/assessments, Africa Medicines Regulatory Harmonization (AMRH)

### 1. Introduction

In sub-Saharan Africa, the lack of harmonized technical requirements and capacity for medicines registration is a significant barrier that prevents access to essential medicines and health technologies. To ensure the safety and health of its citizens, each country must regulate the pharmaceutical products distributed within its borders, conducting a rigorous scientific assessment during the registration process to ensure all medicines meet critical standards of quality, safety, and efficacy. However, many National Medicines Regulatory Authorities (NMRAs) in Africa struggle to meet these important obligations, stemming from challenges including but not limited to shortages of human resources, technical capacity, and funding. The registration process for key essential medicines may be extremely lengthy, stretching

over a period of years, and regulators may not have the capacity to fully ensure acceptable standards are met [1]. As a result, essential medicines are oftentimes less available in African countries than in other markets, despite significant need, and individuals may be at risk of harm from substandard, spurious, falsely labelled, falsified, and counterfeit (SSFFC) medical products. These shortfalls cost millions of lives, and contribute to poor health outcomes and lower life-expectancy relative to other regions of the world.

Over the last decade, African regulators and the international community have come together to address this issue. Given limited resources available to local NMRAs, key opportunities exist to combine efforts through collaborative registration procedures, in which NMRAs can inform their own assessment process by drawing on 1) joint review processes conducted together with other countries in their region, and/or 2) assessments done by the World Health Organization (WHO) Prequalification of Medicines Program (PQP) and/or stringent regulatory authorities (SRAs). Recent successes in accelerating registration processes through these procedures represent an important step towards facilitating access to essential medicines and improving health. Based on this premise, this article will provide:

1. A background on the development of collaborative procedures for medicines registration
2. An overview of procedures currently in place and their applications
3. A closer look at a specific application of collaborative registration and its outcomes.

## **2. Background**

### *2.1. Development of regulatory harmonization efforts & joint review processes*

In the past, the approximately 50 NMRAs in Africa have worked independently to register medicines, with different agencies applying different administrative procedures and technical requirements. The diversity and opacity of these processes have significantly delayed manufacturers in bringing key medicines to local markets in an efficient and timely manner [2]. In 2008, WHO members at the 13<sup>th</sup> International Conference of the Drug Regulatory Authorities (ICDRA) requested that the WHO support harmonization approaches enabling NMRAs to use their limited resources more effectively [3]. In response, the WHO initiated a series of discussions with global partners that led to the formation of a high-level alliance between the New Partnership for Africa's Development (NEPAD) Agency, the WHO, the Bill & Melinda Gates Foundation (BMGF), the World Bank, the UK Department for International Development (DfID), and the Clinton Health Access Initiative (CHAI) [3]. This consortium established a trust fund to support a new initiative, the African Medicines Regulatory Harmonization Initiative (AMRH) [4].

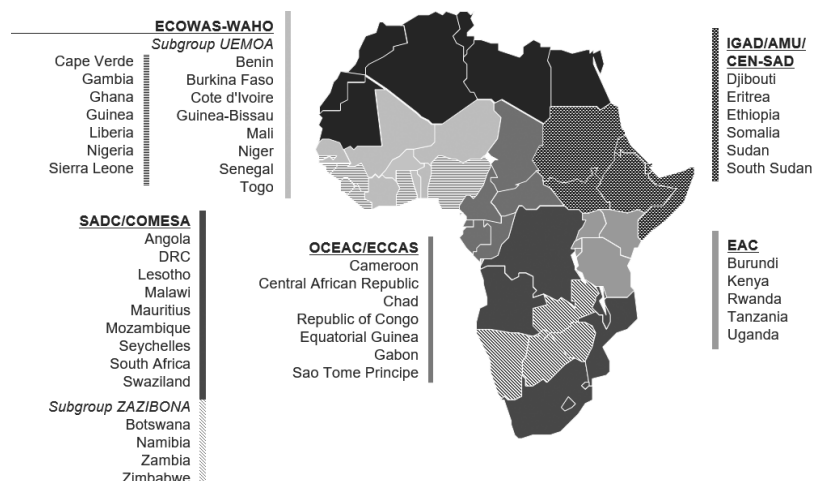


Fig. 1. AMRH Regions. Source: NEPAD Agency.

The goal of the AMRH consortium is to achieve a harmonized medicines registration process in countries belonging to the Regional Economic Communities (RECs), based on common documents, processes, and shared information systems. AMRH is coordinated by NEPAD and implemented with support from partner organizations, particularly the WHO as the primary technical partner. Working with RECs and individual countries, the WHO provides technical assistance in the development and implementation of harmonized approaches for the registration of medicines, supporting overall capacity building, training, and joint activities [3].

Since its establishment, five RECs have begun engagement with AMRH, each at different stages of the harmonization process (see Fig. 1). The East African Community (EAC) was the first region to officially begin harmonization through AMRH in 2012 and has made significant advances to date. In West Africa, the Economic Community of West African States – West African Health Organization (ECOWAS-WAHO) launched AMRH in February 2015, followed by the Southern African Development Community/ Common Market for Eastern and Southern Africa (SADC/COMESA) in July of that same year. Initial progress has also been made in Central Africa, where the Organization for the Coordination and Control of Endemic Diseases in Central Africa (OCEAC) will hold its first joint assessment in 2016 and its first joint Good Manufacturing Practices (GMP) inspection by year's end, and in North-eastern Africa, where the Intergovernmental Authority on Development (IGAD) is preparing a proposal for participation in AMRH [5]. To date, joint review processes for medicines registration have been successfully implemented in the EAC region and in the ZaZiBoNa sub-region, comprising Botswana, Namibia, Zambia, and Zimbabwe.

## *2.2. Development of collaborative procedures with WHO PQP and SRAs*

In addition to collaborating with other regulatory agencies in the region, NMRAs in sub-Saharan Africa have begun drawing on the work of international bodies, such as SRAs or the WHO PQP. In 2010, a WHO assessment of medicines regulatory systems in 26 sub-Saharan African countries found that few NMRAs effectively leveraged WHO PQP to improve registration processes. In response, the WHO developed guidelines for a Collaborative Registration Procedure (CRP) for WHO-prequalified products, designed to accelerate registration through improved information sharing between the WHO PQP and local NMRAs [1]. Subsequently, the WHO, with the support of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), developed similar guidelines for collaborative registration, drawing on assessments conducted by SRAs.

## **3. Joint registration procedures**

### *3.1. EAC joint assessment*

EAC member countries Kenya, Tanzania, Uganda, Rwanda, and Burundi were the first to initiate substantial harmonization efforts under the AMRH initiative in 2009. To facilitate collaborative registration processes amongst member countries, the region quickly developed the following tools:

1. An agreed common technical document for registration of medicines
2. A quality management system implemented in each of the EAC Partner States' NMRAs
3. A platform for information sharing on dossier assessments
4. A framework for mutual recognition of regulatory decisions made by the NMRAs of other EAC Partner States

With these key elements in place, EAC countries developed a joint assessment procedure and, with WHO support, launched an initial pilot in 2011 of two pharmaceutical products. The joint assessment procedure was designed to focus on high-priority medicines, including medicines from the essential medicines lists of member countries and medicines considered lifesaving commodities by the UN Commission on Life Saving Medicines for Women and Children, among other criteria [6]. In submitting a product for consideration, the manufacturer must consent to information-sharing of dossier assessment results among member countries. Once an application is made, a team of assessors from EAC Partner States jointly conducts an assessment, during which external expertise could be sought from other NMRAs, WHO PQP, and academic institutions under confidentiality agreements [6].

Over the course of several pilots, the procedure resulted in a number of successful joint assessments, initially for generic products: a first pilot in 2010–2011

led to two recommendations for licensing of generic products, and a second joint assessment in 2013–2014 resulted in 5 recommendations for licensing of generic products. Subsequently, in April 2014, the EAC joint assessment procedure was endorsed by EAC Ministers of Health. Following that decision, EAC conducted its first successful joint assessments of innovative biotherapeutic products, with a joint EAC/Swissmedic/WHO Clinical Review in October 2015 of Avastin<sup>®</sup> (*bevacizumab*) 100 mg and 400 mg and Herceptin<sup>®</sup> (*trastuzumab*) 150 mg and 440 mg, resulting in their recommendation for licensing in the EAC [7]. (*For more information on the EAC harmonization and registration process, see additional article on EAC harmonization.*)

### 3.2. ZaZiBoNa worksharing scheme

In 2014, NMRAs in Zambia, Zimbabwe, Botswana, and Namibia (collectively known as ZaZiBoNa) jointly took the initiative to collaborate on medicines registration with support from WHO PQP and the Southern African Regional Program on Access to Medicines and Diagnostics (SARPAM). Other countries such as Malawi, Mozambique, the Democratic Republic of Congo, Tanzania, South Africa, Swaziland, and Lesotho started to participate at a later stage in the process as observers. The process is considered as part of a regional regulatory harmonization effort, aimed at accomplishing five objectives: reducing regulatory workload; accelerating the registration process; strengthening intra-regional partnerships for regulatory collaboration; testing a collaborative registration process that could be scaled to other regions; and providing a regional platform for trainings and collaboration in other regulatory fields [7].

The ZaZiBoNa collaborative procedure consists of a work-sharing process for assessing registration applications incorporating SADC and WHO standards. For a product to be considered, it must be submitted for approval in at least two countries in the group, with special consideration given to medicines that address high-priority therapeutic areas as identified by SADC and the UN Commission on Life-saving Commodities for Women and Children, such as maternal, newborn and child health [8]. Manufacturers must also consent to share information amongst ZaZiBoNa regulators as part of the registration process. Once the process is initiated, the regional group appoints one country to lead the assessment of a given product, known as the “rapporteur”. The rapporteur compiles a draft assessment report that is discussed at a quarterly face to face meeting with all ZaZiBoNa health authorities. Jointly, they come up with questions to the applicant, subsequently relaying and assessing responses. Finally, the rapporteur finalizes a suggested Consolidated Assessment Report (CAR) for the group, whereby each NMRA makes its own decision on the final approval of the considered product [9]. Overall, the process was designed to achieve registration within a total time of 11 months [8].

The ZaZiBoNa registration procedure has yielded substantial success; to date, about 125 generic products have been assessed [10], including anti-infectives, anti-hypertensives, and anti-diabetics [11] as well as one innovative medical product,

Novartis' Coartem<sup>®</sup> (*artemether-lumefantrine*) 80/480 mg [12]. In the process, ZaZiBoNa member countries have continued to build regulatory capacity through regional trainings and to strengthen harmonization by coming to common agreements on critical areas such as data requirements, format, and interpretation methods [11].

### 3.3. Joint registration procedures: Next steps

Moving forward, the successful regional joint registration processes developed among EAC and ZaZiBoNa countries could be considered models to implement in other regional groupings or potentially for the African Medicines Agency (AMA), in order to effectively combine resources, share workload, and facilitate medicines registration. The WHO and other institutions are currently looking to build on this process and support regional harmonization and joint assessment processes in other regions of sub-Saharan Africa as well as around the world, particularly among the Association of Southeast Asian Nations (ASEAN) member states [13].

## 4. Collaborative registration procedures (CRP)

### 4.1. WHO CRP

The WHO CRP was the first CRP to be developed, and was designed to leverage the work of the WHO PQP to support participating NMRAs. The WHO CRP seeks to facilitate and accelerate national regulatory approvals by confidentially sharing specific data on the results of the dossier assessment by the WHO PQP with a NMRA reviewing the same dossier for registration. Participation in the CRP is voluntary for manufacturers and NMRAs, and does not interfere with national decision-making processes and regulatory fees already in place. To engage in the process, interested NMRAs must agree to confidentiality, commit to following the principles of the process, and attempt to make a decision on the registration of a product within a target timeline of 90 days. Subsequently, the manufacturer provides the NMRA with the same product and registration dossier that was approved by the WHO PQP, and WHO PQP confidentially shares the outcomes of its assessments and inspections to support the local NMRA as it makes its decision [14].

Since its initiation in 2012, the WHO CRP has been implemented with substantial success. So far, 28 NMRAs have participated, successfully registering over 110 products – with an additional 85 products in the pipeline – as of March 2016 [15]. Many of these products address key health priorities for sub-Saharan Africa, including [15]:

- 50 products registered for HIV/AIDS
- 22 products registered for tuberculosis
- 20 products registered for malaria
- 17 products registered for reproductive health



- 1 product registered for a neglected tropical disease

The WHO CRP has also reduced registration timelines significantly. Over half of all WHO CRP registrations have been successfully completed within the target timeline of three months, with nearly three-quarters in less than four months [15], and median registration time has fallen considerably as the program has matured [7].

#### 4.2. SRA CRP

Following its experience implementing a collaborative registration procedure for WHO-prequalified products, in 2014, the WHO began developing and piloting a similar procedure to draw on the assessment and inspection outcomes from SRAs with the support of the IFPMA [16]. Through the SRA CRP, the manufacturer agrees to share detailed assessment and inspection outcomes from a consenting SRA with the support of the NMRA(s). Consequently, for a product to be considered via the SRA CRP process, pharmaceutical companies and the SRA must consent to information exchange with the NMRA(s) to which a product has been submitted for regulatory approval; similarly, NMRAs must agree to protect sensitive data and ensure its confidentiality. With these preconditions in place, the NMRA is able to draw on data belonging to the SRA in considering a product for approval. The SRA CRP has been piloted for the first time together with the European Medicines Agency (EMA) and Janssen, the Pharmaceutical Companies of Johnson & Johnson, for the pediatric formulation of the antiretroviral INTELENCE™ (*etravirine*) 25 mg oral tablet [17]. Currently, there are four additional drugs being piloted in collaboration with EMA and the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom as the participating SRAs.

### 5. Case study of SRA CRP Pilot

#### 5.1. INTELENCE™ 25 mg oral tablet (Janssen, the Pharmaceutical Companies of Johnson & Johnson)

##### 5.1.1. Background

At the end of 2014, IFPMA sent an expression of interest to all of its member companies to propose drug candidates for the first WHO-facilitated SRA CRP pilot; the pediatric antiretroviral, INTELENCE™ (*etravirine*) 25 mg oral tablet, manufactured by Janssen, the Pharmaceutical Companies of Johnson & Johnson, was selected. The pilot aimed to accelerate dossier review through the use of the SRA Common Technical Document (CTD) adapted for collaborative procedures and GMP inspection waivers, as SRA inspection reports were available for reference. Additionally, dossier reviews were conducted in parallel to other processes (i.e., mandatory sample lab analysis) rather than sequentially, contributing to overall efficiency.

The pilot began in March of 2015 in 11 African countries, with submissions in two waves (see Fig. 2):



Fig. 2. SRA CRP participating countries by wave.

- WAVE 1: Botswana, Democratic Republic of Congo, Namibia, Zambia, and Zimbabwe
- WAVE 2: Burkina Faso, Cameroon, Côte d'Ivoire, Kenya, Tanzania, and Uganda
- OBSERVERS: Rwanda, Burundi

#### 5.1.2. Dossier contents

The contents of the adapted SRA dossier included modules 1, 2, and 3, annexes (including commitments and data sharing authorizations), and a limited number of samples. Module 1 consisted (among other documents) of the Quality Information Summary (QIS-SRA template, available on the WHO PQP website) as well as full EMA assessment and inspection reports. This format of the dossier – the content of which is aligned with initial submission dossiers for the EMA – was well accepted by the NMRAs, though some countries requested additional documentation (e.g., a local application form); most accepted the provision of this additional documentation during the review and not at initial submission.

### 5.1.3. Review process

In March 2015, WHO facilitated initial face-to-face meetings with NMRAs from ZaZiBoNa and the Democratic Republic of Congo; in May 2015, similar meetings occurred with NMRAs from the countries of the EAC and French West Africa. Prior to the meetings, a rapporteur country was assigned for each wave and was tasked with an initial review of the dossier. The rapporteur countries were also responsible for facilitating mutual understanding during the NMRA meetings and honing in on common issues deserving attention. Following the initial meetings, the WHO acted as a facilitator, providing Janssen with questions submitted by the NMRAs. Some NMRAs sent deficiency letters, with one providing some additional country-specific requirements. In order to save time, Janssen submitted responses to all NMRAs independent of whether they sent a deficiency letter or not. Afterwards, Wave 1 and Wave 2 countries met again with the WHO to discuss the responses submitted by Janssen.

### 5.1.4. Approvals

On 4 June 2015, INTELENCE™ 25 mg oral tablet received its first approval in a pilot country within the target window of 90 days from initial submission. As of the date of publication of this article, a total of nine approvals (including both Wave 1 and Wave 2 countries) have occurred within one year of submission, with two additional outlier countries for which registrations are still pending. In one case, the registration certificate was not issued immediately after the positive opinion, creating a delay in completing the registration process. In the other outlier country, GMP inspection was not waived despite the availability of an EMA inspection report. Overall, the median approval timeline across the nine countries was seven months – a significant reduction from the 20-month median timeline cited in a recent BMGF study as a basis for comparison [18]. The result of the pilot has been positive, demonstrating that accelerated registration procedures in Africa involving SRAs are possible, though shorter timelines will likely be targeted in future pilots.

### 5.1.5. Lessons learned and considerations for future pilots

1. **Communication and collaboration between NMRAs:** The review process served as a positive experience for all, especially the less-experienced NMRAs, which stood to benefit from engaging with more experienced NMRAs. Moreover, the face-to-face meetings led to increased dialogue between regulators – for example, about different practices used by each country in dossier review (e.g., the number of samples required). Throughout the process, the WHO served as a vital link between the NMRAs and Janssen, facilitating trust, providing guidance at every step, and enabling a faster flow of administrative tasks. During reviews, the WHO guided discussions among NMRAs to reach a common opinion and provided much sought-after technical input.
2. **Benefits and limitations of using the same dossier for all countries:** From the perspective of the manufacturer, the reviewers were thorough, giving adequate time to respond, and a significant amount of time and resources were

saved because the same dossier was submitted to all countries and a consolidated list of questions was received from all NMRAs. However, it was also apparent that the SRA reports did not reflect some of the on-the-ground realities in some of the pilot countries. In the future, it may be helpful for these reports to include additional information relevant to the African context (e.g., stability data meaningful to resource-limited settings). It might also be useful to consider the inclusion of a bridging report in the submission dossier (i.e., a summary prepared by the manufacturer) to ensure that necessary locally-relevant details are provided to the NMRA.

3. **Suggestions for overall process improvement:** Several suggestions for future pilots emerged from an analysis of this case study. First, it would be advisable for any variation already approved by the SRA and annexes of the assessment reports to be added to the dossier at initial submission to avoid the need to provide this information during the review period. Moreover, there is a clear need to establish a direct line of communication between the applicant and a focal person at the NMRA to facilitate faster follow-up and information sharing during the process. Importantly, to ensure approvals are granted within the outlined timeframe, strict deadlines for phases of evaluation and the provision of responses should be set at the outset and a clear face-to-face meeting calendar established with the NMRAs.

## 6. Additional SRA CRP pilots

Following the success of the SRA CRP pilot for Janssen's INTELENCE™ 25 mg oral tablet, the regulatory harmonization community has begun to leverage available resources and expertise to apply the SRA CRP beyond the individual country level and adapt it to harmonized joint review processes at the regional level.

At the end of 2015, the IFPMA sent an expression of interest to all of its member companies to propose drug candidates for a second WHO facilitated SRA CRP pilot. As high-priority new therapies addressing important disease areas, PREZISTA™ (*darunavir*) 400 mg oral tablet and PREZISTA™ 100 mg/ml oral suspension – both Janssen antiretrovirals – as well as SIRTURO™ (*bedaquiline*) 100 mg oral tablet, the company's anti-TB medicine, were selected as candidates, among others. Both products have been submitted as part of the EAC and ZaZiBoNa joint assessment processes, "fast-tracked" with SRA CRP support.

Submissions for PREZISTA™ 400 mg oral tablet and 100 mg/ml oral suspension began in November 2015 for joint assessment by ZaZiBoNa countries. The first submissions for the SIRTURO™ 100 mg tablet began in February 2016 and are being considered jointly by EAC countries as well as Ghana, Nigeria, Cameroon and Ethiopia [19]. Reviews are ongoing.

## 7. Conclusion

As demonstrated by successful pilots, including that of Janssen's INTELENCE<sup>®</sup> 25 mg oral tablet, the potential benefits of collaborative registration procedures are significant and include reducing the time and costs of regulatory approvals for NMRAs and manufacturers alike. Most importantly, these streamlined procedures can positively influence health outcomes, enabling quicker access to quality medicines for patients in need. Moving forward, regional joint assessment processes have the potential to increase efficiencies in regulatory processes by empowering NMRAs to combine resources and share workload.

The strengthening of these mechanisms in the EAC and ZaZiBoNa regions, as well as potential expansion to other economic communities, represents an important opportunity to build collective local regulatory capacity. Similarly, collaborative registration provides a mechanism to leverage the expertise of SRAs and the WHO PQP program to fast-track registration. Used together, these procedures enable local NMRAs to draw on both regional communities and international support to access to much-needed innovative pharmaceutical products.

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## Policy considerations for originator and similar biotherapeutic products

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Biotherapeutic products (BTPs), also known as biotherapeutic medicines, contain structurally complex active substances produced by living organisms. Due to their complexity and method of manufacture BTPs require distinct regulatory approval standards relative to chemically-synthesized small molecule medicines. This is also relevant for licensing copied versions of a BTP, or similar biotherapeutic products (SBPs) made by a different manufacturer where regulatory concepts developed for generics should not have been applied. In all these licensing scenarios regulators need to evaluate the results of comparability exercises, including sensitive head-to-head analytical, pre-clinical and clinical comparisons with the original product as a basis for approval.

SBPs do not contain chemically identical active substances, and may have slightly different benefit-risk profiles, therefore it is necessary to monitor post-approval safety on a product-specific basis. Policymakers may therefore emphasize the need for product-specific identification in patient records and safety reports using either a unique trade name or a distinguishable non-proprietary naming system. The unique nature of BTPs also informs the nature and degree of interchangeability between the originator and SBPs versions. Many policymakers also emphasize that switching between SBPs should only occur with the involvement of the prescriber. It is recommended that pharmacy substitution would only be appropriate when there is a robust framework for a competent authority to assess product-specific evidence of interchangeability. Another challenge is posed by the historical existence in some jurisdictions of copy BTPs that were not assessed according to current regulatory standards. To address this situation the World Health Organization has proposed a regulatory assessment framework wherein the status of such products can be normalized via the orderly submission and review of supplementary data.

Keywords: Biosimilar, biologic, comparability, similarity, manufacturing, non-proprietary names, interchangeability, substitution, pharmacovigilance

### 1. Introduction

Biotherapeutic products (BTPs) are medicines whose active substances are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances, and are produced by living organisms (such as cells, yeast and bacteria). They are larger and more complex than chemically-synthesized small molecule

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Table 1  
Unique complexity of biotherapeutic products (BTPs)

	Chemically-synthesized small molecule medicines	BTP
Starting materials	Chemicals	Living organisms (cell lines)
Raw materials	Chemicals	Complex media
Manufacture	Chemical synthesis followed by relatively simple purification	Cell culture followed by relatively difficult purification
Active substance characteristics	Low Molecular Weight (typically < 1000 Da) Single, high purity molecular entity  Fully characterized Relatively stable	High Molecular Weight (typically > 10,000 Da) Complex, heterogeneous mixture of product-related substances Partially characterized Relatively labile

medicines, and their characteristics and properties are typically dependent on their source living organism and manufacturing process. This complexity makes the full characterization of BTPs particularly difficult. Chemically-synthesized small molecule medicines are instead medicines whose active ingredients are produced through a step-by-step chemical synthesis process. They are derived from structurally simple chemical compounds with smaller molecular weight compared to BTPs. Therefore, BTPs cannot be copied like small molecule drug products because of their complexity (see Table 1).

A similar biotherapeutic product (SBP) is defined as a product that is similar to an already authorized originator biotherapeutic product, with demonstrated similarity to the latter in terms of quality, efficacy and safety assessed through direct (head-to-head) comparisons. SBPs are also referred to as biosimilars, follow-on biologics, and subsequent entry biologics.

In 2006, the European Medicines Agency (EMA) was one of the first regulatory authorities to develop guidelines and create standards for licensing SBP [1]. The World Health Organization (WHO) published its “Guidelines for the evaluation of similar biotherapeutic products” in 2009 [2].

They were closely followed by Canada [3] and the United States (US) [4] guidance in 2010 and 2015 respectively. Many other national regulatory authorities (NRAs) also have developed national regulatory pathways for SBP registration encouraged by the WHO document.

## 2. Similarity as a distinct concept from generic identity of active ingredient

As their name implies, SBPs are “similar” but not identical versions of their innovative reference biotherapeutic product (RBP). Whereas producing generic versions of off-patent chemically-synthesized medicines is relatively easy – it involves copying a stable chemically-synthesized molecule with a single identifiable structure – producing an SBP is far more complicated due to the complex molecular structure



and the unique manufacturing process required for BTPs. Indeed, unlike chemically-synthesized medicines, it is impossible for SBPs to be exact copies of the RBP. It is important to note that using terms “biogenerics” or “generic biologicals” for SBPs is incorrect simply because it isn’t possible to directly recreate the same molecule.

### **3. Manufacturing changes in complex proteins**

BTPs, being made using living systems, are more sensitive to changes in manufacturing and handling conditions than are small molecule medicines made using relatively straightforward chemical synthesis processes. The quality attributes of a BTP are determined by a wide range of factors, which include the active substance manufacturing process as well as the drug product formulation and fill-finish steps. Small changes in manufacturing can therefore alter the final product. The high complexity of this process requires precision, conformance to good manufacturing practices and defined specifications in order to maintain the safety and efficacy of the product over time. Over 250 in-process tests are carried out for a BTP, compared to around the 50 done for a chemically-synthesized small molecule medicine [5].

Medicinal products are manufactured by a diversity of techniques and processing steps, which depend on the unique molecular characteristics of the product. During the life-cycle of a product, manufacturing process changes or other changes to the approved medicinal product are frequently needed for many reasons, including to: a) make the production process more efficient or the product more pure, at higher yields or with higher quality; b) increase manufacturing capacity (scale-up); c) move the production into a new or different facility (ensuring continuous supply); d) incorporate technical or scientific progress (e.g., improved analytical methods); e) implement changes that are consequential to changes made by suppliers of active substances, excipients, raw materials or packaging materials; f) comply with new regulatory requirements; and g) supply the medicinal product in a new dosage strength, delivery device, or under a new formulation.

Enabling development and post-approval changes is the use of comparability exercises evaluating before and after samples for any significant protein profile differences that may predict different safety and efficacy outcomes.

### **4. BTPs comparability/SBPs similarity exercises for evaluating manufacturing changes**

#### *4.1. Comparability exercises for changes by the same manufacturer*

Comparability is the exercise that will demonstrate that pre-change and post-change versions of a product have a similar profile in terms of quality, safety, and efficacy [6,7]. ICH Q5E restates that comparable does not mean identical [8]. “The

demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.”

The extensiveness of the comparability exercise can depend on the step of the process where the change is being introduced, plus the nature and number of changes being implemented. Comparability exercises often rely on the incremental nature of a given change and are supported by historical experience with the product and process to inform a risk-based assessment. Process-related data plus the post-change product quality attributes and impurities are compared to an extensive history of process and product knowledge by the same manufacturer. A critical element of the exercise is the analytical assessment in which post-change samples, enough to represent the consistency of the change, are compared in side-by-side assays with samples representing the pre-change process.

Many times the analytical assessment of the change is enough to establish the comparability of the product. When residual uncertainty remains and the analytical assessment is insufficient to establish comparability then preclinical and/or clinical evaluation may be necessary. The essence of the comparability exercise is that process-related, analytical and any additional comparisons should demonstrate that the post-change process continues to be representative of the clinical trial material used to establish the safety and efficacy of the product.

#### *4.2. Similarity exercises for abbreviated development of SBPs*

A SBP will most likely have differences in manufacturing processes, raw materials and equipment relative to its RBP. The “similarity” exercise is adapted from the concepts developed for the same-manufacturer comparability exercise, but differs in the balance of risk and required evidence. The manufacturer, lacking knowledge of the RBP manufacturing details, must therefore rely on comprehensive testing including analytical, non-clinical and clinical studies to establish comparability/biosimilarity. The incorporation of similarity exercises to regulate SBPs is vital to ensure that the quality, safety and efficacy are highly similar to those of the innovator RBP. This risk-assessment process must ensure that there are no clinically meaningful differences with the RBP before the SBP receives marketing authorization, thus minimizing risks to patients.

SBP similarity exercises rely on a foundation of structural and functional studies including tailored preclinical and clinical programs which should be considered a sequential process.

“The scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given BTP and for the development of a SBP are the same. Even so, data requirements for the latter are higher and, at least in the EU, always include clinical studies because, due to the completely independent

manufacturing processes, some differences between the SBP and the RBP can be expected, and the potential impact of these differences on safety and efficacy cannot be predicted from analytical assessment alone. . .” [9].

Regulatory decisions have to take all the comparative data into account evaluating each step to determine the extent of uncertainty to be addressed by the next step in the program. This assessment is done through a stepwise exercise, the main objective of which is to demonstrate biosimilarity. These exercises start with a comparison of the quality characteristics of the intended SBP against those of the RBP utilizing a suitable set of sensitive assays covering physicochemical and biological properties. Routine and extended characterization tests are normally used in these exercises which may include stability and degradative studies.

Once high similarity is demonstrated at the quality level, the assessment continues with comparative targeted pre-clinical and clinical studies utilizing relevant and sensitive assay systems, patient populations and clinical endpoints having the intention to exclude relevant differences in the safety (including immunogenicity) and efficacy profile of the SBP compared to the RBP. This means that patients can expect a comparable clinical profile between the two medicines.

#### *4.3. Ongoing life-cycle management for RBPs and SBPs*

After receiving a marketing authorization an SBP sponsor may seek to make post-approval changes that should be assessed using the above-mentioned “same manufacturer” comparability framework. Such post-approval comparability assessments for either the SBP or the RBP should demonstrate that significant changes have not taken place impacting clinical safety and efficacy performance thus avoiding product divergence and concerns over biosimilar designation [9].

## **5. Regulatory and policy challenges**

### *5.1. Overview of assessments*

A comprehensive similarity exercise is required to ensure the safety and efficacy of SBPs, which should thus be regulated via pathways that are distinct from those applied to generic medicines.

SBPs must be evaluated on the basis of a rigorous regulatory pathway to ensure that they demonstrate high similarity in quality, safety, and efficacy to an approved RBP. The RBP should be carefully selected to ensure that it has been licensed on the basis of a full dossier and that its benefit risk profile is well established. As outlined in the preceding section the biosimilar regulatory pathway should require the sponsor to provide evidence of similarity from a stepwise similarity exercise. That exercise should include comparative analytical characterization of the proposed SBP and an appropriate RBP and comparative non-clinical and clinical studies.

Regulators will recognize that even comprehensive analytical characterization using state-of-the-art technology may not identify all differences between a proposed SBP and the RBP. When analytical studies reveal differences it may be challenging for sponsors and regulators to assess their clinical relevance. Therefore, uncertainties regarding the biosimilarity and the clinical implications of differences found will remain and must be investigated through additional comparative pre-clinical and clinical studies.

Immunogenicity in human subjects/patients cannot be predicted from analytical and non-clinical studies, and immunogenicity profiles may differ between the SBP and RBP. Thus, it is important for the sponsor to develop and qualify sensitive and robust immunogenicity assays and to provide a comprehensive comparison of clinical immunogenicity. Clinical comparability studies are typically limited in scope and duration, so a more complete assessment of the SBP's benefit-risk profile with respect to immunogenicity may require post-marketing experience. Regulators should take these points into consideration in evaluating the evidence from the clinical comparability studies and the proposed risk management plan for the SBP.

Finally, given the complexity and sensitivity of BTPs and the fact that products from different manufacturers may differ in subtle fashion that might impact their benefit-risk profile, a robust pharmacovigilance system is a key component of a science-based regulatory pathway for all BTPs, including SBPs.

Some considerations for regulatory systems to enable a robust SBP regulatory framework [10]:

- 1) Establish a regulatory framework that is distinct from that for generic chemically-synthesized small molecule medicines.
- 2) Require that sponsors of the SBP select an appropriate RBP approved on the basis of a complete dossier for use in comparative studies.
- 3) Require that the proposed SBP and the RBP can be demonstrated to share the same mechanism of action (to the extent known), dosage form, strength, and route of administration.
- 4) Require that sponsors of SBPs demonstrate a comprehensive understanding of the physicochemical and biological characteristics of the SBP and RBP through thorough comparative analytical studies.
- 5) Require sponsors of SBPs to confirm high similarity of the proposed SBP to the RBP in terms of safety and efficacy through appropriately designed tailored non-clinical and clinical studies.
- 6) Require that immunogenicity of the proposed SBP be adequately evaluated (i.e. in an appropriate number of patients to permit the detection of differences in the types and rates of immunogenic events) pre-market and also appropriately evaluated post-market, and compared to that of the RBP.
- 7) Provide for mechanisms to ensure clear prescribing, dispensing, use and pharmacovigilance of SBPs once marketed (e.g., clear labeling, unique identifiers, patient and physician education, and an appropriate pharmacovigilance plan).

## 5.2. Non-proprietary naming

BTPs have never quite followed the traditional drug naming paradigm of using the active ingredient's international non-proprietary name (INN) [11,12]. Although several non-glycosylated biotherapeutic classes (e.g., insulins or somatropins) have shared INNs, many glycosylated biotherapeutics (e.g., epoetins, follitropins) have INNs with unique Greek letter suffixes. These distinguishable INNs are determined according to WHO's policy that applies a distinguishable Greek letter suffix to the INN for each new version of a glycosylated biotherapeutic [13]. This policy is based on the assumption that glycoproteins manufactured using fundamentally different cell substrates and culture processes will likely have unique glycosylation patterns. A second distinction is that versions of BTPs have typically (but not always) been marketed using proprietary trade names, departing from the common generic drug labeling convention.

The development of SBPs has stimulated policy debates regarding whether to apply the generic drug naming paradigm or to apply a modified approach. The generic drug naming paradigm might encourage the perception by patients and prescribers that SBPs have identical active substances and could therefore be used interchangeably with the originator product. Published surveys provide evidence that some prescribers may make such inferences [14]. Furthermore, prescriptions using the INN instead of a brand name might be fulfilled at the pharmacy using any version of the product. Such "generic prescribing" is encouraged for chemical drugs. These perceptions and practices might therefore promote higher utilization of SBPs, much as they do for generic drugs.

However, some policy makers recognized that policies and practices used for generic drugs might conflict with safe prescribing and use of BTPs. Versions of BTPs are not considered to have identical active substances and may not be fully interchangeable at the individual patient level. Many jurisdictions encourage prescribers to be involved in decisions to prescribe a specific version of a BTP, and prescribing by INN is discouraged. Finally, it is generally agreed that post-marketing safety surveillance for BTPs should be tracked and analyzed at the individual product level [2]. There are concerns that, absent specific policies for BTPs, a shared INN might permit a high proportion of ambiguously attributed safety reports.

SBPs were originally licensed in Europe in 2006, and since that time WHO, the biotherapeutic industry and drug regulatory agencies have considered various policy alternatives for naming of BTPs. These policy options include use of unique trade names, use of the WHO INN Greek letter policy, special INN naming rules for SBPs, development of various national nomenclature policies, and a proposal for a universally available biological qualifier issued by WHO.

### 5.2.1. Trade names

Reflecting that BTPs are often marketed with unique trade names, Europe has formally adopted a policy that SBPs should have the same INN as the RBP, but that

Table 2  
Trade name attribution of biotherapeutic-related adverse event reports in pharmacovigilance systems

Product class	Region and timeframe	Trade name attribution (%)	Reference
Insulin	US 2005 to 2013	84%	Stergiopoulos et al., 2015
Somatropin	US 2005 to 2013	92%	Stergiopoulos et al., 2015
	Europe 2004 to 2010	91%	Vermeer et al., 2013
Filgrastim	Europe 2004 to 2010	85%	Vermeer et al., 2013
	Australia 2011 to 2014	58%	Amgen Inc., 2015
Erythropoietin	Europe 2004 to 2010	99%	Vermeer et al., 2013
Monoclonal antibodies	Netherlands 2009–2014	67%	Klein et al., 2016

each BTP should have a unique trade name [15]. This policy is supported by EC pharmacovigilance legislation requiring member states to take measures to ensure that prescriptions, patient records, and adverse event reports should refer to BTPs using the trade name [16].

Use of biotherapeutic trade names in adverse event reports is not universal and can vary according to the product class and region. Published data covering US, Europe and Australia show that use of trade names in adverse event reports varies from 58% for filgrastim products in Australia [17], 67% for monoclonal antibody therapeutics in the Netherlands [18], 84% for human insulin in the US [19], and greater than 90% for somatropin and epoetin products in Europe (see Table 2) [20].

While ambiguous product traceability in a portion of adverse event reports has not been associated with signal detection failures in the aforementioned countries it has been a serious issue in Thailand. Thai authorities were unable to identify the suspect product causing a cluster of pure red cell aplasia (PRCA), a serious adverse event, in patients receiving versions of epoetin alfa. At the time of the PRCA cluster more than a dozen originator and copy versions of epoetin alfa were marketed in Thailand, and medical records did not differentiate use of these products according to trade name [21].

### 5.2.2. INN Greek letter suffix

Sponsors for two SBPs of epoetin alfa followed WHO INN guidelines for glycosylated products and applied for new INNs with a distinct Greek letter suffix: epoetin kappa (SBP authorized in Japan) [22] and epoetin zeta (SBP authorized in Europe) [23]. The WHO summarized this application of existing INN policy to SBPs following an INN Program Open Session in 2012 [24]. However, this practice is voluntary and uniform application of the Greek letter policy would rely on drug regulatory agencies to enforce WHO INN policies rather than permitting pro-forma use of the reference product INN.

### 5.2.3. National non-proprietary naming policies

Pending a final nomenclature policy from WHO several regulatory agencies proposed or implemented unique national naming systems covering SBPs. The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) implemented a sequential

suffix approach wherein each subsequent SBP to a given RBP has a non-proprietary name comprising the INN followed by the designator “biosimilar” and a serial number indicating order of authorization, e.g., “Epoetin Alfa Biosimilar 1” [25,26]. In 2013 the Therapeutic Goods Administration (TGA) in Australia proposed using a compound suffix comprising the letters “sim” followed by a 3 letter qualifier unique to each SBP, e.g., “infiximab simfam” [27]. The TGA proposal was suspended in 2015 pending discussion of the WHO Biological Qualifier program [28].

The US Food and Drug Administration (FDA) also evaluated several approaches to differentiated naming, not necessarily limited to SBPs. In 2013 FDA authorized a non-biosimilar version of filgrastim using a 3-letter prefix in the non-proprietary name “tbo-filgrastim” [29]. Subsequently, FDA has proposed via draft guidance a system using a 4 letter suffix to be applied to all BTPs [30]. The first two FDA-licensed SBPs have proper names “filgrastim-sndz” [31] and “infiximab-dyyb” [32], and in 2015 FDA indicated via a proposed rule [33] that it intended to retrospectively modify the names of RBPs expected to be subject to biosimilar competition.

#### 5.2.4. *Biological qualifier*

Taking into account the various options considered during consultations, as well as the emerging proliferation of national naming schemes, WHO proposed in 2015 to create a globally available biological qualifier (BQ) [34]. The BQ is proposed as a 4 letter code of random consonants, with a potential option of including a 2 digit “check sum” that could be used to verify the code integrity. The BQ would be an additional and independent identifier used in conjunction with the INN to facilitate product identification in prescriptions, patient records, and pharmacovigilance reports. The BQ would be administered by the WHO INN Programme on a voluntary basis and codes could be assigned to any biological substance having or eligible to have an INN. Unique codes could be assigned to each version of a biological substance that is manufactured by a corporate body using a single process and under the oversight of a global quality system.

As of mid-2016 the BQ program had not been implemented, and WHO was considering options for a pilot implementation program involving several member states [35].

#### 5.2.5. *Summary of naming policies*

The introduction of SBPs has stimulated policy debates about the appropriate approach to ensure that products are properly identified in prescriptions, patient records, and adverse event reports. WHO and drug regulatory agencies agree that use of the INN is not appropriate for identifying BTPs, but there is disagreement about measures to ensure differentiation. Use of trade names is generally encouraged, but some jurisdictions may prefer to supplement this approach with a system of distinguishable non-proprietary names or qualifiers. The WHO Biological Qualifier program may offer a universal approach to assigning such qualifiers.

## 6. Interchangeability and substitution

The term “interchangeability” has a variety of meanings, depending on the policy framework that applies in a given jurisdiction. In one sense, the term conveys that a product may be expected to have a similar benefit-risk profile to another product in the same therapeutic class when used to treat a given medical condition. Such products may be therapeutically substituted with the involvement of a prescriber. In another sense, the term is used to indicate that a product is therapeutically indistinguishable at the patient level and hence may be substituted without the knowledge or intervention of a prescriber. Clearly, these two concepts cannot be captured in a single policy framework and it is important to differentiate them when covering the topic of interchangeability.

### 6.1. *Interchangeability with respect to formulary and procurement policies*

In the context of procurement and formulary practices, “interchangeability” often refers to the concept that two or more products are considered to be therapeutic alternatives in a given indication. Typically, such product classes would have the same mechanisms of action and would provide a comparable risk-profile at the population level. This concept may apply to any member of a therapeutic class (e.g., statins, anti-TNFs) and would, by definition, include SBPs and their RBPs, given that SBPs must have the same mechanisms of action and similar safety and efficacy in their approved indications. Indeed, a consensus report prepared by the European Commission defines interchangeability for SBPs to be “The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber” [36]. Here, we refer to this version of interchangeability as “medically-guided interchangeability”.

According to the aforementioned definition, several European drug regulatory agencies have communicated that “interchangeability” is implicit in the approval as a biosimilar, meaning that patients may be initiated on or switched to the SBP with the involvement of the prescribing clinician, but not via pharmacy substitution [37]. In practical terms, drug procurement and formulary practices that would leverage medically-guided interchangeability to encourage use of SBPs are beyond the jurisdiction of drug regulatory authorities.

### 6.2. *Interchangeability with respect to enabling pharmacy substitution*

In a more stringent sense, interchangeability is understood to apply to a framework permitting substitution at the pharmacy level. For example, generics are considered therapeutically equivalent to their respective original brand medicines such that they may be safely substituted for the brand without the prior approval of the prescribing



clinician. Here, we refer to this version of interchangeability as “pharmacy-mediated interchangeability” [38].

There is currently no consensus regarding whether approval as a SBP is sufficient to permit pharmacy substitution, or whether additional evidence and risk assessment may be necessary on a product-specific basis. Accordingly, WHO SBP guidance states that such (pharmacy-mediated) interchangeability is beyond the scope of its scientific guidance and should be determined by competent authorities in member states [2]. Similarly, EMA guidance states that interchangeability should be determined at the European Union member state level [1]. Health Canada has indicated that approval as a Subsequent Entry Biologic (SEB) does not merit claims of bioequivalence or clinical equivalence [3]. Furthermore, given that biotherapeutic quality profiles can evolve over time, interchangeability assessments may not be durable and Health Canada therefore does not support pharmacy substitution [39]. The US FDA has stated that it is concerned about “inadvertent substitution” of non-interchangeable SBPs, reflecting its view that biosimilarity by itself is not sufficient to justify pharmacy-mediated interchangeability [30].

Notwithstanding the aforementioned disclaimers from WHO, EMA, Health Canada, and the US FDA several competent authorities are implementing pharmacy-mediated interchangeability frameworks that would permit pharmacy substitution of designated SBPs. For example, the enabling legislation for the biosimilars pathway in the US includes a provision for a regulatory determination of interchangeability in addition to the biosimilar pathway [4]. In 2015 the Australian Pharmaceutical Benefits Advisory Committee (PBAC) issued a policy memorandum stating that it could designate SBPs as suitable for pharmacy substitution, a policy measure known in Australia as “a-flagging” [40]. In both examples the competent authority (the US FDA or the PBAC, respectively) may assess additional evidence on a case-by-case basis to determine whether a given SBP is suitable for pharmacy-mediated interchangeability.

### 6.3. IFPMA position

In May 2016 the International Federation of Pharmaceutical Manufacturing Associations (IFPMA) published a position paper recommending elements of a sound policy framework for pharmacy-mediated interchangeability [38].

- 1) The specific SBP has received a formal interchangeability designation, contingent upon a competent authority performing a risk assessment establishing that the SBP is interchangeable with its RBP. The basis of the interchangeability assessment should be transparent to payers, patients and health care providers;
- 2) The SBP meets the regulatory requirements to be able to be approved for all indications of the RBP such that exclusions should thus only exist only for administrative or legal reasons (for example, intellectual property);

- 3) For BTPs that typically are administered multiple times in the course of treatment, the interchangeability designation should be justified including clinically relevant evidence that switching or alternating between the SBP and RBP would not impact safety or efficacy;
- 4) Legal frameworks have been established to permit the substitution of designated interchangeable SBPs while allowing the prescribing physician the 'right-to-refuse'; and
- 5) The jurisdiction has established a robust pharmacovigilance system, including adequate reporting of adverse events. Furthermore, the patient, pharmacist and the prescribing physician can readily access (for example via patient health records) unique identifiers for the dispensed BTP, including a unique product identification and batch information, so as to support pharmacovigilance.

#### 6.4. Summary of interchangeability policies

There has been significant debate and divergence among stakeholders regarding the appropriate role of prescribers and pharmacists in determining which version of a BTP should be administered to a patient. During the initial period after SBP entry in Europe some policymakers cautioned that SBPs should be used to initiate treatment naïve patients, but not necessarily to switch patients who were already stable on an originator brand. In 2015, several drug regulatory agencies clarified their positions to encourage medically-guided switching. In reality, such practices were occurring all-along in some jurisdictions or markets that employed tender-based, single-source procurement policies.

Policymakers distinguish between such medically-guided interchangeability and policies that would permit substitution at the pharmacy level. Laws and policies in the US and Australia now permit substitution of designated SBPs following a case-by-case evaluation by a competent authority. Elements of these interchangeability evaluation frameworks may include assessments of whether the SBP may have a disproportionate risk in certain populations and of data supporting switching between the originator and SBP.

The IFPMA recommends that interchangeability frameworks should include case-by-case assessments by a competent authority. Furthermore, the IFPMA supports pharmacy practice policies that preserve a prescriber's option to preempt a substitution. To support a robust pharmacovigilance system, IFPMA believes that patient records should include accurate and complete information about the specific product dispensed and, furthermore, that these records are readily accessible to the prescriber and patient as well as the pharmacist.

### 7. The issue of non-comparable biotherapeutics products (NCBs)

As science-based pathways specific to the development, registration and surveillance of SBPs come into existence, some NRAs are still in the process of adapting their regulatory frameworks for BTPs. As a result, there are some countries

Table 3  
Global situation for existing regulatory pathways

Countries where similar biotherapeutic product (SBP) guidelines have been adopted		Countries where SBP guidelines have not been adopted
<b>Non-comparable biotherapeutic products (NCBs) that were approved before the implementation of country-specific SBP guidelines, and the product is currently in the market as approved by NRAs according to prior local regulations (e.g., generic or abbreviated pathway).</b>	<b>NCBs that are approved after the implementation of country-specific SBP guidelines based on an alternate or abbreviated pathway that has been adopted by the NRA.</b>	<b>NCBs are approved as stand-alone products</b> and the data meet neither the WHO SBP Guidelines nor the standard for newly developed innovative BTPs. Clinical equivalence trials are not performed.

where intended copy biotechnological products have been licensed under regulatory pathways that are not appropriate for BTPs, such as (a) those that were intended for generic, chemically-synthesized pharmaceuticals, (b) abbreviated pathways requiring very minimal data, or (c) pathways where standards for approval are not well-defined (see Table 3). In these instances, the lack of specific guidance based on science-based assessment that is in line with the WHO Guidelines [2,41] on the Evaluation of Similar Biotherapeutic Products (2009) means that BTPs not shown to be comparable to a suitable RBP have been approved in certain markets. These NCBs belong to such classes as: interferons, erythropoiesis stimulating agents (ESAs), colony stimulating growth factors (CSFs) and somatropins. Monoclonal antibodies and fusion protein products have also been approved by these abbreviated pathways non-compliant with WHO guidelines.

NCBs are medicinal products that are developed without a complete comparability exercise even though a full regulatory data package of quality, safety and efficacy studies is sometimes provided. In contrast to SBPs, NCBs have not been shown to be similar in all three of these fundamental areas to a licensed RBP as defined by WHO guidelines. It is this totality of evidence that enables a SBP to establish a relationship to data originally generated for the originator RBP. In some cases, however, the sponsor of a NCB utilizes the safety and efficacy profile of another product rather than generating independent, substantive clinical evidence. Table 4 shows the differences with respect to quality, safety and efficacy data requirements between an RBP, an SBP meeting WHO expectations and associated guidelines, and a NCB at the time of market authorization application.

Since there is neither substantive stand-alone data nor sufficient evidence of similarity for a NCB, the basis of approval of such products is likely questionable. On the basis of this data gap, the balance of benefit versus risk is, in most cases, unknown resulting in substantial uncertainty. Consequently, there is little basis for reference to the safety and efficacy profile of another product and thus it is not surprising to see an increasing number of publications suggesting quality differences and lack of similarity between different NCBs and the RBP [42]. More recently safety signals

Table 4  
Data requirements at time of marketing authorization

Data category	Reference Biotherapeutic Product (RBP)	Similar Biotherapeutic Product (SBP)	Non-comparable Biotherapeutic Product (NCB)
Quality	Full stand-alone quality data set.	Full stand-alone quality data set <i>plus</i> comprehensive side-by-side testing showing similarity to an originator RBP. Clinically meaningful differences not identified. Evidence of high degree of similarity is the basis for reduced non-clinical and clinical requirements for licensing.	Scope of quality data unknown. May not include any side-by-side assessment showing similarity to the originator RBP.
Safety	Full stand-alone non-clinical and clinical safety data, including immunogenicity assessment.	Side-by-side non-clinical and clinical safety data, including immunogenicity assessment, supporting claim of biosimilarity. Data generated in a comparative fashion on both SBP and RBP.	Scope of safety data unknown. May not include any side-by-side assessment showing similarity to the originator RBP. May only include very limited (or no) immunogenicity data.
Efficacy	Full stand-alone data set from pivotal efficacy trials.	Targeted clinical program comprising of comparative pharmacokinetic, pharmacodynamic, and efficacy trials, statistically powered to establish non-inferiority or equivalence to the RBP, which is included in the trials.	May include no or only very limited clinical data. Studies may not be powered to establish non-inferiority or equivalence to the originator RBP. Originator RBP may not be included in the clinical trial(s).

have been associated with their use, such as the pure red blood cell aplasia (PRCA) cases detected in Thailand [21].

### 7.1. The regulatory assessment of approved BTPs as an opportunity to tackle the issue of NCBs

The issue of approved BTPs not complying with WHO regulatory standards discussed above, and that many countries are impacted, is recognized by WHO. In their recently published guidance on “Regulatory assessment of approved rDNA-derived biotherapeutics” WHO is encouraging NRAs to undertake a stepwise regulatory review of all BTPs already authorized in their specific market by [43]:

- 1) Identifying the products that have been licensed with data which do not meet current WHO regulatory expectations.
- 2) Assessing the identified products and gaps, based on the product-specific considerations in order to decide the appropriate action to remedy the situation and

the timelines for implementing this action involving a risk-benefit assessment of the situation.

The product manufacturers should submit to the NRA within a short period of time a plan of action including an analysis of available and missing data in accordance with WHO guidelines as well as a description of measures, which may include interim assessments and proposed timelines, needed to address the identified gaps. It is further recommended that NRAs should assess the incoming data (e.g., quality/manufacturing, nonclinical and clinical data as needed) in a stepwise approach in several separate packages at different times – and on the basis of the outcome should decide on appropriate regulatory action e.g., whether or not the product license can be maintained.

In order to decide if a particular licensed product should be allowed to remain on the market during the review process described above the WHO document is proposing a risk assessment performed by the NRA taking into account among other factors:

- 1) The number of products on the market which have been licensed without adequate quality, nonclinical and/or clinical data.
- 2) The availability of alternative therapeutics on that market licensed locally with an adequate data package and/or also by an experienced NRA, meeting the standards of the relevant WHO guidelines.
- 3) The extent of the use of a BTP as well as availability of alternative products.
- 4) The seriousness of a potential lack of efficacy.
- 5) The ability of the pharmacovigilance system in the country should be considered to monitor and determine adverse reactions and/or efficacy problems.

Following through systematically with this concept will enable NRAs to properly mitigate the risk associated with NCBs but not leaving patients without treatment at the same time.

### *7.2. Capacity building and transparency as the key challenges for regulatory agencies in the upcoming years*

Considering all the above, agencies specifically those in low and middle income countries may have difficulties – from a capacity and capability perspective – to follow up properly with all regulatory demands associated with BTPs and SBPs. In respective guidance documents [43] it is suggested that WHO and agencies experienced in the regulatory evaluation of BTPs should mentor less experienced agencies. Inter-agency trainings including the shared review of submissions may be considered. Also the exchange of assessment reports under confidentiality arrangements may be considered an option.

The mid or long term goal would be that currently affected agencies will be able to help each other and eventually move into a work-sharing mode analogous to those implemented in the EU. One of the key components to make this happen is regulatory convergence. Another recommendation [43] is the sharing of information

between NRAs regarding the basis for regulatory decisions on BTPs and SBPs e.g., via publicly available evaluation reports. This will build confidence in each other's capabilities and as a consequence the trust to potentially rely on each other's decisions.

The summary basis of decision documents of Health Canada, the EMA or the US FDA are examples of highly elaborated informative documents. Other agencies like MFDS from South Korea in 2014 or ANVISA from Brazil in 2015 also started the publication of summary assessment reports advancing an initiative from IPRF (International Pharmaceutical Regulators Forum) to propose a template for a "Public Assessment Summary Information for Biosimilars" (PASIB) that should help regulatory agencies to produce a standardized English language summary of their assessments of SBPs. In their implementation guidelines the IPRF is proposing a document based on WHO terminology that should be composed of three sections [44,45]:

- 1) Administrative information: Mainly completed by the applicant, this would contain details of the SBP and the RBP, the indications applied for, compliance with legal requirements, and links to additional information published by the NRA.
- 2) Data submitted and reviewer summary: The dossier and data content part would be filled in by the sponsor, and the review details by the authority. The quality part section would include the identification of analytical methods "at a high level, respecting confidentiality issues".
- 3) Reviewer conclusions: This section would contain concise high level conclusions to convey the basic information, such as whether the biosimilarity exercise was considered acceptable. It can mention areas where issues were raised during the review, and indicate whether all the claims proposed by the sponsor have been accepted (extrapolation of indications, for example). "Sufficient reasoning should be included in the PASIB to convey the outcome to a knowledgeable reader".

IPRF is encouraging NRAs who do not currently publish their reviews to engage in this initiative. Communicating details of what information was reviewed and how it was incorporated into decision-making may be also important for prescribers, patients and other stakeholders and can help them gain confidence in BTPs [43].

## 8. Conclusions

BTPs contain structurally complex active substances produced by living organisms. Due to their complexity and method of manufacture BTPs require distinct regulatory approval standards relative to chemically synthesized medicines. These considerations apply to originator medicines as well as to intended copy versions. The WHO and many NRAs have established guidelines or regulations concerning the

comprehensive similarity exercise needed for the development of SBPs. Implementation of these frameworks can be challenging, and must also consider mechanisms to normalize the regulatory status of historically licensed NCBS.

Policy makers are assessing measures to facilitate product-specific pharmacovigilance of BTPs. Policy makers and stakeholders are also considering the appropriate terms of use for SBPs, including whether patients may be switched to SBPs with the involvement of the prescriber or via pharmacy substitution.

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## Import testing turned into an unnecessary limitation of patient access to medicines as risks are managed effectively

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The presented facts suggest that import testing does not protect patients. On the contrary, it introduces potential risks to access of medicines and reduces the remaining shelf life time of medicines driving possible drug shortage. In the absence of data proving the evidence that import testing is decreasing risk to patients, if manufacturers comply with the evolving Good Manufacturing Practices (GMPs) and Good Distribution Practices (GDPs) regulations, including secure supply chains with documented controls, import testing should be waived. In these cases, importing country's Health Authorities should be confident the product is safe, of high quality, and in compliance with registered specifications.

This article presents risk assessments demonstrating that product quality is continuously controlled. Moreover, import testing does not detect counterfeit or substandard products nor reduces the additional risks related to local distribution channels, as testing occurs at the point of entry into a country.

Keywords: Import testing, importation, testing, Good Manufacturing Practices (GMPs), Good Distribution Practices (GDPs), risk assessment

### 1. Introduction

This article reviews the developments in the regulatory environment since import testing was introduced in the European Union (EU) legal framework as well as other countries and postulates that such import testing introduces additional risks to patients.

Prior to being accessible to patients, pharmaceutical products undergo well defined procedures on registration according to regulatory requirements (Fig. 1). If the marketing authorization is granted, manufacturing and packaging is performed in accordance with regulations specific to GMPs. Finally the product is tested to assure it meets approved product specifications prior to its release to the market. The legal requirements for the release formally differ from country to country. However the market release decision is a holistic decision by an 'independent quality unit',

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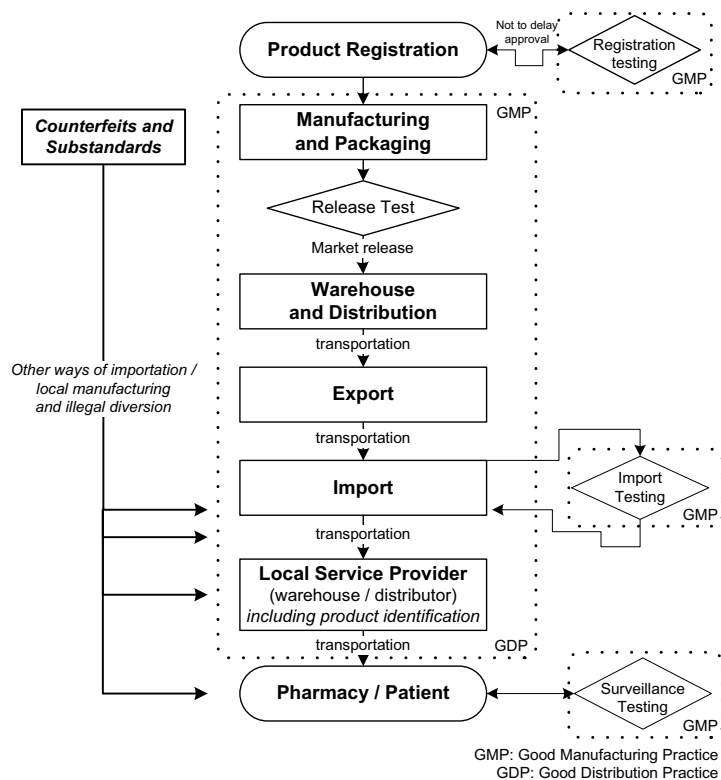


Fig. 1. Product flow and related testing activities.

which can be represented by an ‘authorized person’ (AP – World Health Organization (WHO) terminology)/ ‘responsible person’ (RP – Pharmaceutical Inspection Co-operation Scheme (PIC/S) terminology)/ ‘qualified person’ (QP – EU terminology). The decision to release considers all available information on the performance of the operation during a given cycle of manufacture for final disposition.

After the release, the product is stored in a warehouse, ready for distribution. Recent changes in legislation added additional supply chain oversight assuring appropriate storage and transport conditions to maintain product quality in accordance with GDPs requirements (e.g., in the EU [1]). In addition, repackaging/relabeling operations follow GMPs. During transport the product is exported from country A and imported into country B. A Local Service Provider (LSP) or a manufacturer’s own local operation performs the product identification and quality check of the inbound shipment (e.g., based on monitoring data) and organizes the transport of the product to a hospital/pharmacy to be available for the patient (Fig. 1).

Throughout this very well controlled and regulated process for the legitimate supply chain, safe and efficacious medicines are delivered in a timely manner to patients.

A series of additional controls are required in several countries/markets before marketing (registration testing) and at the end of the supply chain (surveillance testing) to protect patients (Fig. 1).

In spite of full compliance with current regulations, good quality practices, all the procedures and controls mentioned above, an additional test is required in many countries: the repetition of the release testing upon importation – referred to as ‘import testing’ [2]. This article demonstrates, to the best of our knowledge, the lack of documented evidence that import testing reduces risk or uncovers any additional risks, which usually occur later in the supply chain (e.g., manufacturing steps performed in the country of destination) or identifies counterfeits and/or substandard products introduced by using different means of importation (e.g., parcel post).

## **2. History of import testing**

In 1975, the EU introduced the requirement to repeat all tests, when a drug (medical) product is imported (see 75/319/EEC Article 22 [3]). It is recognized that import testing requirements may have been necessary in the 1970s as a result of the limited development of regulations, alertness and enforcement procedures in the supply chain of pharmaceutical products. Since then, many countries outside the EU have implemented, or are considering putting into place, import testing requirements.

The pharmaceutical industry is following contemporary and enforced GMPs and GDPs regulations published and maintained by, e.g., the EU [1] and the United States (US) [4] as well as WHO [5] and PIC/S [6]. Holistic controls are introduced into the supply chain, e.g., in the EU with the Falsified Medicines Directive [7]. Furthermore, industry develops and implements robust quality management systems describing all procedures and additional holistic controls [8]. These defined and controlled procedures contribute to assure supply chain integrity, safety, purity, and potency of drug products.

Today, increased regulatory supervision and enforcement of the manufacturers by frequent regulatory agency inspections [9] are in place. The AP/RP/QP in a quality unit with independent oversight, also makes the requirement of import testing in the middle of the supply chain irrelevant. The objective of ensuring product quality and patient safety at the end of the supply chain when delivered to the patient is not affected. Thus, import testing can be regarded as redundant and unnecessary step, a view shared in the position paper developed by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) [10].

More and more countries are now, however, requiring and/or enforcing import testing by implementing additional regulations. This trend does not correlate with the increasing understanding by National Regulatory Authorities (NRAs), of the need for globally harmonized requirements and procedures following best practices and

continued improvements based on experience. There is no data available demonstrating any real patient impact if the additional requirement of import testing is implemented. To understand this contradictory development, the research-based pharmaceutical industry gathered data on testing, requirements, efficacy of import testing and the associated business impact. This analysis includes obvious and hidden costs related to import testing [2].

### 3. Current legal situation

The requirements for importation testing are described in the legislation of the EU and other countries. Opportunities applied for waivers and implemented flexible approaches show the uncertainty of the need for an import testing requirement.

#### 3.1. EU legislation

The Article 51 (1b) of the EU Directive 2001/83/EC [11] sets a requirement for import testing and states: “In the case of medicinal products coming from third countries irrespective of whether the product has been manufactured in the community, that each production batch has undergone in a member state a *full qualitative analysis*, quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of the medicinal products in accordance with the requirements of the marketing authorization (MA).” [11].

Article 51 (2) [11] allows exceptions to import testing by stating: “In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community, and to ensure that the controls referred to under point (b) of the first subparagraph 1 [see above] have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls” [11]. A respective “appropriate arrangement” is already established in the EU Directive 2011/62/EU [7]. Upon request, exporting countries are included in the list referred to in Article 111b, if the “country’s regulatory framework applicable to active substances exported to the Union and the respective control and enforcement activities ensure a level of protection of public health equivalent to that of the Union”.

Subsequently the EU-GMP directive 2003/94/EC [12] and related guidelines in EudraLex Volume 4 (EU-GMP) [1] further specify the expectation on implementation of import testing requirements according to article 51 (1b) [11].

#### 3.2. Import testing requirements in other countries/regions

Markets other than the EU adhere to import testing requirements potentially without considering the progress industry and regulatory requirements have made by

implementing risk control measures and following international quality standards. Garbe et al. [2] describe 34 countries (the EU market is counted as one country) with import testing requirements, and the several types of waivers applied for following legal, regulatory, compliance and practical approaches.

### 3.3. Related registration testing requirements

In many countries, additional registration tests have to be performed prior to the Marketing Authorisation (MA). Registration testing is often used to establish product specific infrastructures, including test methods for import testing or for market surveillance studies (MSS) in governmental laboratories. In some countries, this testing can delay the approval process of new medicines up to 22 weeks [2]. Similar delays may re-occur in the case of assessing post-approval changes and when licenses/authorizations are renewed. Moreover, registration testing results in administrative bureaucracy with its respective financial impact.

### 3.4. Applied opportunities for flexible interpretation in regulatory statutes

Waivers from import testing may be possible even in countries where routine import testing is the rule. Allowing flexible interpretation within the legal environment could enable the regulatory statutes and guidelines to focus resources on patient protection. The EU-GMP Annex 16 [13] and the draft concept paper on a guideline on importation of medicinal products (potentially Annex 21) [14] are demonstrated examples of using the EU regulations to potentially support waivers by flexible interpretation.

Trade relationships between the EU and US increased for the benefit of both economies. Considerable changes are required in the EU to consider that the regulatory oversight is equivalent in other regulatory jurisdictions [15]. In the EU “*appropriate arrangements*” (e.g., Mutual Recognition Agreements – MRA) are operational and include the waiver of import testing for products imported from Australia, Canada, Israel, Japan, New Zealand and Switzerland [16].

## 4. Additional risks introduced by import testing

Today, risk-based approaches are required to control the quality of medicines. This risk assessment looks at the risks associated with import testing: “*Does import testing reduce the risk for patients receiving medicines?*”.

### 4.1. Challenges in meeting demands – A practical example

The start of the drug product manufacturing defines shelf life time, i.e., time period for which a drug can be stored or used, for a batch of the medicinal product.

Table 1  
Examples of RSTs required by selected countries, e.g., used in tender orders

Remaining Shelf Life Time [RST]	Countries
75%	Bahrain, Kazakhstan, Kuwait, Oman, Russia, Saudi Arabia, Ukraine
70%	Iraq
66%	Algeria, Egypt, Iran, Jordan, Lebanon, Lybia, United Arab Emirates, Morocco, Qatar, Tunisia, South Africa (depending on products types)
50% or less	Bosnia & Herzegovina, Israel, Macedonia, Turkey
More than 6 months	China, EU (most countries)

Subsequently the primary manufacturing itself, release testing, batch release process and the secondary manufacturing has to be performed. The drug is ready for patient usage when, as an example, two months of the shelf life time has already passed. In order to prevent drug shortage situations, a manufacturer must build up considerable safety stock throughout the supply chain. Since the best practice in warehouse management utilizes a “first in – first out” principle, safety stock will have used up these four months from the shelf life time of the product (Fig. 2).

The health care systems in the countries where governments are responsible for ordering and importation of pharmaceuticals are acting more and more with ‘tender orders’ (e.g., in the Middle East/Africa region, by hospital pharmacies). These special orders are usually placed by a government to obtain a high volume of drugs by a specific date. Certain requirements apply and can be predefined by local laws. Generally, these requests are placed on an annual basis and require up to 75% Remaining Shelf Life Time (RST – Table 1).

Industry generally understands the reason for the RST requirements in tender orders. However, this practice has a huge impact on the supply chain management of products with a shelf life time of less than 36 months. Extra resources are allocated and principles/good practices (e.g., “first in – first out”) are typically violated in order to meet these demands in the supply chain for delivery to patients.

#### 4.2. Barriers to access due to stock in quarantine

On average, import testing takes about four weeks to complete [2]. As a consequence, blocked stock in the specific country reduces the RST as time elapses in quarantine. In some instances, this loss could be longer than the four weeks, if there is additional handling of goods (e.g., sampling). Experience shows that at least six weeks lead time must be added for manufacturing (secondary packaging), release testing by the manufacturer and forward shipping. This lead time can translate up to a delay of 10–12 weeks during which the finished product cannot be used. Additional delays occur, if secondary manufacturing is also performed in a third country requiring import testing, or even if such a country is used as a distribution hub for a region (Fig. 2).



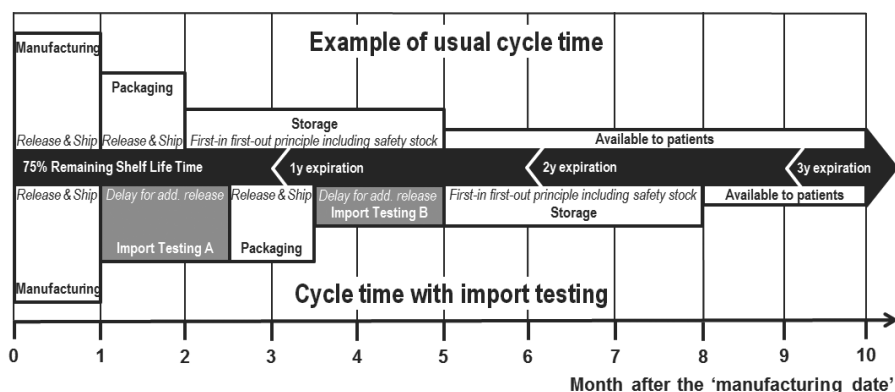


Fig. 2. Example of cycle time in the supply chain with and without import testing in relationship to the RST.

These circumstances are additional, but unnecessary, factors to be considered when evaluating risks of drug shortages [17]. Consequently, the root cause for drug shortages of more stock under quarantine can only be avoided by using time consuming planning, preventing unnecessary quarantined stock and by intensive communication with health authorities in affected countries. These block resources on industry and regulators side, which can be used better for controls which more efficient demonstrate patient safety.

#### 4.3. Risk of drug shortage

By the very act of the import testing, drug products are blocked in quarantine and therefore are not readily available for delivery to patients in a timely manner. Furthermore already released drug product is consumed in the testing process. In addition to the testing itself, reserve and retention samples reduce the availability of the drug product to the legitimate supply chain. These samples can accumulate up to a loss of 1,020 packs per batch of medicinal product. This sample volume is calculated as follows: 1) it is assumed that a company serves all the 34 countries/regions requiring import testing [2] and two of these countries have a site for secondary manufacturing and/or are used as a hub for regional deliveries; 2) five packs are used per import test; and 3) an additional ten reserve/retention samples are required, e.g., for repeated testing in the scope of investigations. In some cases even considerably more sample packs are required, especially for inhaled products. If an individual shipment contains drug product from multiple batches, the amount of testing and samples is increased.

The value chain of a commodity needed as starting material for an Active Pharmaceutical Ingredient (API) and/or the final drug product may take up to two years. If the demand increases, it can take that long until additional drug products can be

delivered in the supply chain to patients. As a consequence, additional resources have to be spent by regulators and industry to develop and agree on exceptions (e.g., allowing supply of registered products from other markets, parallel trade).

#### *4.4. Missed chances in ecological risk management*

Any ecological benefits are lost as repeated testing requires resources such as reagent, equipment, and power. The environmental impact is negatively increased by the use of electrical power, water, and disposable plastics as well as toxic/radioactive materials. Most of these materials cannot be recycled and additional waste is created.

#### *4.5. Economic risk management for a better protection of patients*

In a competitive environment, economic benefits are of importance to companies, and an import testing waiver could decrease overall manufacturing costs. The resources spend for import testing today could be re-absorbed, bring more efficiency to the supply chain and regulatory processes and better used to control and combat the illegitimate supply chain (e.g., detection of counterfeits and substandard products), for example, by extending Market Surveillance Studies (MSS) using identification tests to better protect patients in the local market.

To estimate the financial expenditures used to comply with import testing, a survey was conducted by the European Federation of Pharmaceutical Industry and Associations (EFPIA) in 2015. As an example, imports from the US to the EU were assessed along with the number of batches subjected to retesting in one year. 15 multinational EFPIA member companies (i.e., Almirall, Amgen, BMS, Chiesi, GSK, J&J, Les Laboratoires Servier, Merck-Serono, MSD, Novartis, NoviPharma, Novo Nordisk, Pfizer, Roche, UCB) responded. In addition, the survey covered the cost for analytics as well as administrative and overhead costs associated with import testing (also refer to [2]). Ten companies reported 8,495 affected batches with five companies not importing any batches on the EU-US route.

The following calculations for the estimated financial expenditures are based on the reported average direct costs of €2,950 per imported batch [2]. These costs include resources for the analytical testing of every imported product.

In general, the resources for maintaining an import testing program can be broken down as follows (approximate figures):

- 65% Direct costs spent for the analysis and technical personnel (see [2])
- 25% Costs for additional administration (e.g., Quality Management System owners/managers, sample management, record and document management, IT/Laboratory Information Management Systems (LIMS) maintenance)
- 10% Overhead costs for people management, training and audits/inspection management

The second and third bullets above (25% and 10%) represent additional costs, which were not considered in the survey [2]. For the total cost assumption, further costs are detailed as companies have to provide additional support for the import testing when contract or government laboratories are used (e.g., the Official Medicinal Control Laboratories – OMCL – network organized by the European Directorate of Medicines – EDQM). These additional resources can include, for example, on-going activities and consumable items such as:

- Analytical method transfer and method validation (including implementation of changes in pharmacopoeias)
- Reference standards (including preparation, certification and supply)
- Reagents (including qualification prior to use)
- Test equipment (e.g., high performance liquid chromatography columns) including calibration/maintenance
- Training of testing staff (agency and/or contractor)
- Additional in-country stability testing, as required
- Shipping costs of samples
- Managing the importation of all required materials according to specific country requirements
- Need for additional material in the supply chain for a specific country to compensate shortened Remaining Shelf life Time (RST)
- Materials on the market with a low level of RST and potential need for replenishment
- Laboratory infrastructure

What if these additional costs are also taken into account? On average, the costs estimated for the above activities is around €1,100 per re-test (full analysis) and has to be added to the reported [2] direct average cost of €2,950.

*What if the costs of blocked capital are included?* Nine companies reported the loss of €37,672,259, representing 18,616 analyses, due to the prolonged quarantine (e.g., quarantined in warehouses, at customs, etc.) of medicinal products. These figures may be used to estimate blocked capital of an additional €2,024 per batch analysis, even though no direct correlation has been made. The impact of all of these costs per analysis, i.e., direct cost of €2,950, plus indirect and hidden costs of €1,100, plus the losses due to blocked capital of €2,024, accumulates to €6,038 overall cost per analysis.

Overall, considering the analysis of the 8,495 batches reported, this represents resources equivalent to €50,970,000. This significant sum is what these 10 companies reportedly spent on import testing in one year. This estimate covers only the import testing from US into the EU. These companies represent about 31% of the market value of the research-based pharmaceutical industry [18]. Assuming the relative trade is constant among pharmaceutical businesses and these companies are a representative portion of the overall market, the estimated total costs for import testing aggregates to €164,419,355. Considering this amount represents the cost of import testing for products imported from the US into the EU only, the global spending for import testing is assumed to be inestimably higher.

#### *4.6. Further risks in the supply chain*

To some extent sampling and storage may occur in the legitimate supply chain where GMP and GDP may not be applied to all aspects on the supply chain (e.g., under quarantine in customs/bonded warehouses). As a consequence, a less stringent chain of custody may increase the risk for test samples to not be representative, lost or diverted. In addition security/tamper-evident seals of the products may need to be broken. As a consequence, replacement of seals is not traceable and a risk for contamination is presented. Furthermore, interim storage in warehouses may increase the risk for temperature deviations [2]. However, the consistent oversight of the manufacturers ensures the detection of any transport deviation, if occurred. If not covered by stability data, a deviation will result in a rejection of the material, even very late in the supply chain.

#### *4.7. Outcome of the risk assessment*

The assessment of the hazards associated with import testing demonstrates that routine import testing is not an appropriate control to be considered in the light of global supply chains and implementation of best practices (e.g., GMP and GDP).

### **5. Risk controls implemented to facilitate waivers for import testing**

Modern pharmaceutical manufacturers are implementing risk reduction measures as part of their continuous improvement programs [19]. They established comprehensive oversight mechanisms for compliance and patient safety along their supply chain. Emerging requirements such as GDPs are also more and more enforced on distributors, traders, and local service providers.

#### *5.1. Compliance risk management in manufacturing and supply*

Manufacturing and distribution occur in a highly regulated environment. There are hazards addressed by NRAs and others, when waiving of import testing is considered, such as:

- Failure to detect issues with the original product quality
- Inadequate release testing
- Failure to detect deterioration on transportation
- Loss of public confidence in imported medicines
- Failure to detect counterfeit finished products
- Potential for disreputable suppliers to provide substandard product
- Loss of economic value in a country/region through the provision of employment

NRAs might try to address risks supposedly coming from these hazards by additional rigid regulations and increasing oversight with additional testing and/or inspections including certification audits. However for these companies complying with the procedures described in a quality management system [19] the remaining risks are considered to be ‘very low’ for all of the provided hazards as presented in Table 2.

### *5.2. Controls of patient safety risk*

Scientific evaluations [2] demonstrate that patient safety is not enhanced by import testing because of the well-established and effective quality management systems employed by industry in the manufacture and supply of medicines. There is no evidence that import testing has any added value to further control imports. In fact, this is supported by analyzing the rejection rate in import testing analyses. This rejection rate was identified to be 0.005% (one rejected batch out of 18,616 tested batches) [2]. It is concluded, that the probability of detecting residual product non-conformance by import testing is very low.

### *5.3. Additional effective risk controls are established*

As a result of the survey, assessments of hazards and implemented controls, it is concluded, that import testing – provided manufacturers comply with good practices (GMPs/GDPs) – does not provide additional control of risks to patients and is therefore considered redundant.

### *5.4. Potential for refocus of import testing resources*

Import testing has a very limited scope and does not reflect the existing situation of the products available to patients in a country or region. Uncertainty about the quality of the domestic distribution system can exist until the product reaches patients. This uncertainty can be better controlled when authorities focus on implementing or extending Market Surveillance Studies (MSS) [20–22]. MSS can be considered the best use of resources for a company, if performed, e.g., for products subjected to a high risk for counterfeits and substandard products. The MSS testing approach represents the unique opportunity to detect quality issues of products on the market. In addition, MSS can detect counterfeits and substandard products before the medicines are delivered to patients, and it does not cause any delays in access of medicines to patients like import testing does. Those countries that carry out MSS testing already have the benefit of still being able to assess product on the market rather than promoting more countries adopting this approach. Import testing, in contrast, considers only lots in the legitimate, established supply chain.

Table 2  
Risk assessment and control grid to support the elimination of import testing requirements

Hazard	Risk assessment		Risk control	
	Anticipated risk	Implemented and functioning risk reduction measures	Residual risk <sup>3</sup>	
Loss of public confidence in imported medicines because of the perception that a control step has been removed.	High	Limited effect because the general public is largely unaware of the current control strategies in the supply chain.	Very low	
Due to counterfeiting issues this may be perceived as a necessary "barrier" by politicians.	High	Appropriate identification testing is implemented upon receiving at the point of importation or at the warehouse.	Very low	
Failure to detect counterfeit finished products, e.g., EU, MRA country are safe countries (with IP laws in place) others may be non-safe countries.	High	Typically a counterfeiter would not introduce product for import testing. Most examples show counterfeit product infiltrates the supply chain during local distribution. These risks might be better tackled through GDP enforcement and serialization and/or surveillance testing. However, the distribution chain via parcel post orders in small portions and/or internet orders provides additional risks. These supply chains are anyway not subjected to import testing.	Very low	
Concern that removal of the retesting activity would mean loss of economic value in a country/region through the provision of employment.	High	This would have an impact but on a very limited number of jobs in any country. An increase of surveillance testing would be more patient focused and even create jobs.	Very low	
Potential for disreputable suppliers to provide substandard product as they know it will not be retested.	High	This should be controlled by the Quality Management System (QMS), GDP and due diligence processes done for all customer supplier relationships.	Very low	
Issues with the original product quality that may not be found.	Medium	Low failure rate for import testing so expected limited impact providing a strong QMS release testing procedures and oversight on all stages of manufacturing processes is in place. Quality has to be produced into the product, not tested at the end only.	Very low	
Failure to detect deterioration on transportation.	Medium	Implemented GDP practices such as temperature monitoring, stability programmers, validated distribution and shipping routes, choice of appropriate packaging components incl. seals/tamper evidence etc. are more effective mechanisms to ensure quality than retesting a small non	Very low	

Table 2, continued

Hazard	Risk assessment		Risk control	
	Anticipated risk	Implemented and functioning risk reduction measures	Residual risk <sup>3</sup>	
An increased number of testing sites would need to be inspected by the authorities – resource risk.	Medium	representative sample of a batch. Inspectorate resources are known to be limited and this could lead to delays in granting import licenses, if an inspection is mandatory for the license. Gaining trust (e.g., via PIC/S) among inspectorates facilitates recognition/reliance opportunities. Reasonable waivers of import testing requirements are implemented and could be better used, as applicable.	Very low	
The elimination of import testing proposal is rejected but awareness has extended oversight to other areas, e.g., stability, API testing.	Medium	Control processes are based on scientific rationales. Import testing is considered as not adding benefit.	Very low	
More emphasis would be placed on regulatory inspections and there may be a concern that a frequency of every two years is insufficient to provide adequate control.	Low	The oversight of the export site is covered by legislation (e.g., EU QP). Consequently the regulatory inspections and the firm's QMS and internal audits should be sufficient to provide assurance. Furthermore these processes are getting more focused and risk based.	Low	

<sup>3</sup>With regards to patient safety when waiving import testing.

## 6. Conclusions and outlook

The presented risk assessments demonstrate that it is highly questionable, whether any risk to patients is reduced by import testing. Quite the reverse, import testing increases the risks to patients by facilitating e.g.:

- Increasing the Drug Shortage risk
- Stock in quarantine
- Reducing RST
- Supply chain complexity
- Pressure on ecological effectiveness
- Misuse of resources and economic losses

The pharmaceutical industry is committed to support all requirements that contribute to reducing or eliminating risks to patients. Waivers of import testing will improve product availability and reduce lead times. A waiver of import testing is secured by manufacturers implementing GMPs/GDPs and therefore enabling uninterrupted supply of products. Keeping the requirements on import testing, which are performed in the middle of the supply chain, can decrease product availability, prolong lead times, and therefore contributes to put the uninterrupted supply of products to patients at risk. An infographic was published to visualize the topic in a simplified manner [23].

### 6.1. Further opportunities using the existing regulatory framework

Comprehensive oversight of manufacturing and supply is well-established. Besides performing manufacturing and release testing, industry provides additional information to regulators in the dossiers, which get approved by the competent authorities for a country or region. Inspection oversight preferably by domestic inspectorates, controls the compliance with GMP and GDP requirements.

Giving the variety of waivers implemented [2] and the results of the assessments discussed in this article, it should be considered to allow the following, for example:

- **Automatic waiver, if the product is manufactured in a recognized country**  
A list of countries is established to waive the import testing requirement based on their legal framework, controls of manufacturing and distribution as well as enforcement policies. In the EU, this approach would be similar to the equivalence of regulatory oversight for the ‘written procedure’ upon importation of APIs [16].
- **Waiving of import testing when shipment validation is performed**  
Shipment validations are confirming oversight of the distribution chains. The initial transport validation would cover the needs to demonstrate that the supply chain is fit for purpose and to guarantee the quality has not changed during transportation.
- **Advance specification settings for import testing**  
The release specification as part of the regulatory commitments could be separated into quality attributes: a) confirming the success of the manufacturing process; and b) confirming the identity of the product (finger print). Only the product identity in b) is tested upon importation and/or surveillance testing (reduced specification). This would be proposed and justified by the applicant in the release specification sections of the Q-CTD 3.2.P.5.1 and 3.2.P.5.6.  
In the EU such separation is already accepted under the conditions of parametric release [24]. Article 51 (1b) of the EU Directive 2001/83/EC [11], as well as Chapter 1.5.4 of the recent EU-GMP Guideline [1] Annex 16, provide a base for reduced specification, stating that a product batch must undergo testing in a Member State “*in accordance with the requirements of the marketing authorisation (MA)*”. In addition, Annex 16 (scope section) states: “*The basic arrangements for batch release for a product are defined by its MA. Nothing in this Annex should be taken as overriding those arrangements*”. Hence, if a reduced specification is approved with the MA, reduced import testing is acceptable. Equally, it would be an appropriate utilization of the directive 2001/83/EC Art. 51(2) [11] to waive import testing requirements if “appropriate arrangements” are established and “equivalent” GMPs standards are applicable to the country of origin.
- **Testing upon registration, post-approval changes and license renewals, if required, is not delaying access of new medicines**  
Without import testing the knowledge can be transferred independent for the registration process to support opportunities, e.g., for MSSs.



## 6.2. Final note

Today, no strong rationale exists to support import testing assuming that pharmaceutical manufacturers follow international good practice standards and have implemented controls of the products and production processes throughout the entire supply chain. Waiving or removing such redundant import testing would significantly reduce product lead times, blocked inventories and the risk of drug shortages, especially on a country level. Accordingly, an uninterrupted supply of important medicines to the patients could be further ensured. Remaining risks related to import testing would be decreased as the robust GDPs would not be interrupted. Resources could be spent in activities such as improved information exchange between regulatory agencies, further reliable inspection schemes by NRAs and, if considered necessary, market surveillance testing. Moreover, continual improvement of supply chain processes can be more efficient. In addition, simplified regulatory procedures will lead to a better control of the local market.

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## Pharmacovigilance: “Vigilantia initiative”

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Every day Pharmacovigilance becomes increasingly important to patient health. There are some gaps and limitations in the current Latin American Pharmacovigilance framework which could be addressed to have a better system to correctly and promptly identify suspected adverse drug reactions (ADR). Considering this context, Vigilantia was born as an initiative to foster Pharmacovigilance both scientifically and educationally, and enhance all aspects of the safe and proper use of medicines, across all Latin America.

Keywords: Pharmacovigilance, patient safety, Vigilantia, adverse drug reaction (ADR)

### 1. Introduction

Pharmacovigilance becomes more important to patient health every day. According to the World Health Organization (WHO), pharmacovigilance plays an important role in protecting patient safety by identifying, quantifying, assessing and preventing risks that arise from the use of medicines. It is a discipline that learns from its own experience, evolves and is re-defined with the arrival of new research data and results. The overall goal of Pharmacovigilance is to accurately and promptly trace a patient’s adverse event to a particular product and manufacturer and to use this information to improve public health by ensuring a positive benefit risk profile for the medicine [1].

According to the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), all biopharmaceutical companies, countries and national regulatory authorities should have appropriate controls and measures in place to perform this important discipline. Recently, the scope of pharmacovigilance has expanded to overlap, in part, with additional activities such as the need to monitor possible counterfeit medicines, the development of good manufacturing practices and the training of healthcare professionals (physicians, pharmacists, and nurses) and stakeholders in good pharmacovigilance practices [2].

All medicines can cause adverse drug reactions (ADR) and certain rare ADRs, undetectable during clinical trials prior to marketing authorization, which are only

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discovered once the medicine is on the market. Moreover, there are some key pharmacovigilance principles to ensure biotherapeutic medicines safety that are important to discuss further. It is critical to manage biotherapeutic medicines correctly because they have unique characteristics. Due to their biological nature and complex structure, biotherapeutic medicines require special ADR tracking. Traceability is vital for correct biotherapeutic management, and for this there has to be a distinguishable name, safe prescription and dispensing to patients, and accurate reporting of suspected ADRs. Prescribing by brand name and distinguishable International Nonproprietary Name (INN) allows physicians rapid access to the precise product dispensed when reporting suspected ADRs.

However, good tracking and tracing practices are not enough for an effective application of pharmacovigilance. It is critical to have a good and well-structured system that facilitates ADR reporting from all sources, including patients and healthcare professionals. In addition, it is also important for some medicines to have a Risk Management Plan (RMP) that proactively plans activities to characterize known risks, identifies new risks, drives increased knowledge about the safety profile of the medicine, and plans and implements risk minimization and mitigation if appropriate. Nevertheless, traceability and an adequate system will be useless if the stakeholders involved do not use these tools adequately. Healthcare professionals should use distinguishable names when prescribing a medicine and key stakeholders should report ADRs in a consistent way to ensure effective pharmacovigilance monitoring [3].

There are some gaps and limitations in the current status of pharmacovigilance in Latin America that could be addressed to have a better system to correctly and promptly identify ADRs. Considering this context, Vigilantia was born as an initiative to foster pharmacovigilance both scientifically and educationally, and enhance all aspects of the safe and proper use of medicines across all Latin America. Vigilantia focuses on three main pillars: 'Pharmacovigilance Training in a Box', a strategic alliance with ISoP (International Society of Pharmacovigilance), and the Peers and Voice initiative. These pillars are further described in this article.

## **2. Background information on pharmacovigilance in Latin America**

The article "Key elements in the establishment of adverse events notification systems in Latin America" from Mira JJ, Cho M, Montserrat D, Rodríguez J, Santacruz J. describes the results of a study which took place in seven Latin American countries (Argentina, Brazil, Chile, Colombia, Cuba, Mexico and Peru) with 17 national experts on adverse event notification and three experts from the Pan American Health Organization (PAHO). In this study the authors analyzed the main characteristics, scope and limitations of the adverse event notification systems in the region [4].

From the study it can be concluded that in Latin America there is a lack of basic pharmacovigilance knowledge among health professionals which means they do not have the necessary background to complete and submit quality suspected

ADR reports. Furthermore, there is no tradition of prioritizing patient safety in Latin America so it is difficult to engage healthcare professionals in pharmacovigilance. These findings show a clear need for improvement of the suspected ADR notification system, focusing on training healthcare professionals on the process [4].

Moreover, IFPMA, in its report "Pharmacovigilance of Biotherapeutic Medicines: Identifying Global Case Studies Illustrating Successes and Challenges" shows that countries like Mexico have been working in developing new systems to engage and encourage patients to report ADRs. This real-life example demonstrates that reporting by patient groups has the potential to increase knowledge about the possible harms of medicines increasing patient's safety [2].

Another important example in IFPMA's report focuses on Brazil, which has adopted patient registries as a post-marketing surveillance tool. BIOBADAMERICA is a tool that collects information on relevant adverse events occurring with long-term treatment with biotherapeutic medicines. This platform allows for continuous online monitoring and facilitates the interaction between pharmacovigilance monitors and collection centers [2].

Hence, there is a clear consensus that all Latin American countries should establish a certification program in order to train experts such as healthcare professionals, academics and regulators, and all stakeholders who might be involved in the process of ADR reporting in basic pharmacovigilance. The successful implementation of new and better pharmacovigilance systems depends on healthcare professionals and national regulatory authorities that are trained in the need, value, and operation of the country's pharmacovigilance system [1].

### **3. Vigilantia**

Vigilantia is an initiative that emerged to respond to the need to improve the Pharmacovigilance process in Latin America. Vigilantia aims to raise awareness and stimulate interest in the importance of patient safety and provides a walk-through of the current Pharmacovigilance practice as well as a description of other related pharmacology topics. The core purpose of this initiative is to stimulate the full and proper use of national ADR reporting systems by training and informing all relevant stakeholders on best practices to protect patient safety.

Vigilantia consists of three main pillars: 'Pharmacovigilance Training in a Box', ISO-P Collaboration and Peers and Voice.

### **4. Pharmacovigilance training in a box**

After careful study, IFPMA concluded in its report that the initiatives to improve pharmacovigilance are only useful if the quality and quantity of the ADR reports are adequate. Therefore, to provide high quality reports, it is key to have healthcare

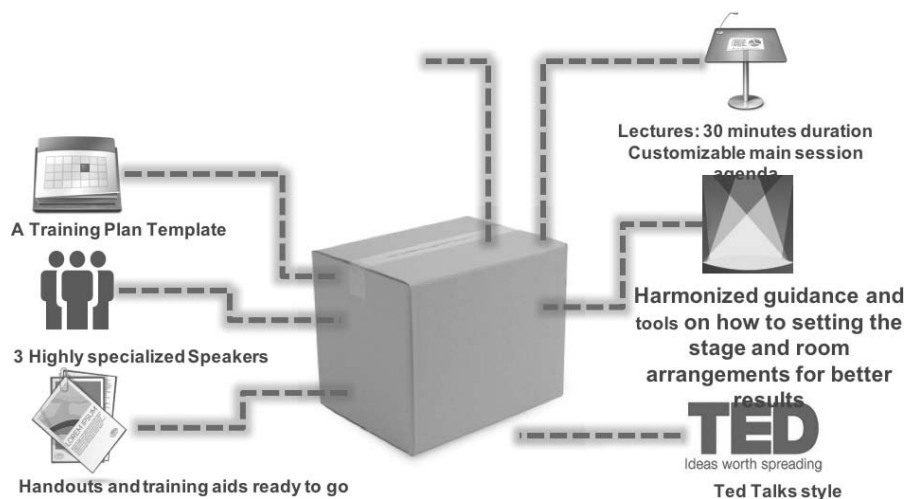


Fig. 1. PV Training in a box. Is the best quality I have, if is not good please remove it.

professionals and other interested stakeholders that understand the importance of pharmacovigilance to patient safety and that adequately report ADRs in a timely manner to improve the quality of information and reporting rates [2].

Pharmacovigilance Training in a Box is an effective training toolkit on basic Pharmacovigilance, modularly assembled as a "One-Size-Fits-All" training to satisfy different stakeholders with a 1-day training session. Figure 1 shows the components of the training kit. The material is clear, concise and interactive which allows any stakeholder to learn the basic aspects of pharmacovigilance in 1 day.

The training comprises two modules: Vigilantia I, which is concerned with basic pharmacovigilance issues; and Vigilantia II, which addresses new concepts related to medicinal products such as biotherapeutic and biosimilar medicines, and the application of pharmacovigilance to this newer category of medicines.

Each segment comprises two chapters: one theoretical and the other practical. The aim of the first chapter is to familiarize stakeholders with pharmacovigilance as a tool for successful medicine management and to educate participants in specific considerations for medicinal products such as biotherapeutics and biosimilars. In the second chapter, the training participants have the opportunity to apply the theoretical knowledge they have learned in the first chapter by discussing real-life experiences and defining positions.

Likewise, Vigilantia II has a theoretical segment where stakeholders learn about innovative biotherapeutic and biosimilar medicines, and the strong link to pharmacovigilance. The practical segment facilitates a space for discussion about the different topics learned.

The Vigilantia Pharmacovigilance Training in a Box is a toolkit that aims to educate stakeholders about pharmacovigilance and its applications in an interactive way.

## **5. Partnership with ISoP**

ISoP is a key partner in the Vigilantia Initiative, and its collaboration has been crucial. In 2009, ISoP created its Latin American Chapter with the objective of developing educational activities with the aim to increase knowledge and to ensure training in the field of pharmacovigilance [5].

Since 2014, ISoP has organized annual meetings, co-sponsored by FIFARMA, to discuss different pharmacovigilance topics. The main objective of these meetings is to foster pharmacovigilance in Latin America by inviting key stakeholders in pharmacovigilance to discuss relevant topics.

Since the creation of Vigilantia there have been two Latin American ISoP symposiums (both supported by FIFARMA). The first one was held in Buenos Aires in 2014 and centered on "Keeping our focus on what matters to patients". The key message of this symposium was "to have a real impact on patient welfare and safety, pharmacovigilance must be an integral part of the healthcare delivery system and also seen as a matter of critical importance for the whole of society".

The second Latin America ISoP symposium took place in Sao Paulo, Brazil in September 2015. This symposium focused on providing a space for multiple stakeholders to discuss drug safety and signal detection from different perspectives to share ideas on how patient safety could be further improved. The scientific program, coordinated by Raquel Herrera Comoglio, was a well-balanced combination of the fundamental basics and practice of pharmacovigilance, as well as the most recent challenges in drug regulation and use [5].

The third Latin American ISoP Symposium will be held in Bogotá, Colombia on August 25 and 26, 2016.

## **6. Peers and Voice**

Peers and Voice is a scientific network with the objective of addressing and amplifying pharmacovigilance topics that have become more of a challenge for healthcare professionals, payers, national regulatory authorities, scientific organizations, universities, state authorities, patient groups and the pharmaceutical industry.

Peers and Voice was created to pioneer pharmacovigilance education and reinforce the need to implement risk management plans for medicines. Peers and Voice is a network that aims to expand pharmacovigilance awareness to diverse types of stakeholders, from consumer groups to NGOs. In January 2016 a strategic "call to action" workshop was held in Buenos Aires with key stakeholders and selected professionals from different regional associations whose objective was to share the Vigilantia Pharmacovigilance Training in a Box materials and to plant the first seed of the Peers and Voice initiative. One of the main results of this meeting was the formation of four working groups led by regional associations with the objective to develop specific projects and key tasks for Vigilantia in each region or country.

## 7. Conclusions

It is clear from this article that pharmacovigilance has become an essential tool to protect patient safety. Everyone should understand the value of reporting and monitoring suspected medicine side effects. Latin America does not have a robust system that facilitates the submission of high quality ADR reports in the region. Therefore, Vigilantia emerges from a need for new or better systems to report suspected ADRs as well as a need to improve regional pharmacovigilance processes. Thus, Vigilantia aims to address these challenges by training key regional stakeholders on good practices to improve patient safety.

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## Counterfeit medicines: Threat to patient health and safety

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Counterfeit medicines are, first and foremost, a matter of patient health and safety. Counterfeit medicines pose a threat to patients because of the conditions under which they are manufactured, in unlicensed, unregulated, uninspected and often unsanitary sites.

The “medicines” themselves pose a threat to patient health and safety because their contents are not regulated and they may not contain the correct active pharmaceutical ingredient (API) to deliver the therapeutic benefit for which they were prescribed, or even ingredients that are themselves harmful such as heavy metals or pesticides.

To mitigate that threat, and ensure that their patients receive safe and effective medicines, pharmaceutical companies have incorporated anti-counterfeiting technologies into their packaging and implemented campaigns to detect and disrupt those counterfeiters who place greed above patient safety.

Although counterfeiting presents a global threat from which no company, therapeutic area, region or country is immune; gauging the true scope of the problem has remained a challenge. There are hopeful signs, however, as we have seen improved reporting and greater transparency by enforcement and regulatory agencies.

Keywords: Counterfeit, spurious, falsified, fake medicines, pharmaceutical crime, legitimate supply chain, patient health

### 1. What’s in a name?

They may be known by many names – counterfeit, spurious, falsified, fake – but the common element to medicines, whether branded or generic, that have been deliberately and fraudulently produced and/or mislabeled so as to appear as a genuine product, is that they pose a threat to patient health and safety. For purposes of this article, we use the term “counterfeit” to refer to those products.<sup>1</sup>

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<sup>1</sup>In an attempt to reach consensus among its member states, in 2012 the WHO adopted the category of SSSFFC (substandard, spurious, falsely labelled, falsified or counterfeit). While all medicines within that category are inherently unsafe, we think it is important to distinguish between counterfeit medicines, as defined above, and those of poor quality (substandard,) if we are to understand the criminal nature and extent of the counterfeiting phenomenon.

Pharmaceutical counterfeiting is a crime of trick and deceit. Counterfeit medicines, and the threat they pose to patient health and safety, are a growing problem from which no country, therapeutic category, or pharmaceutical company is immune.

## **2. Serious threat to patient health and safety and the healthcare system**

Counterfeit medicines are, first and foremost, a matter of patient health and safety. Counterfeit medicines pose a threat to patients because of the conditions under which they are manufactured, in unlicensed, unregulated, uninspected and often unsanitary sites. We have seen “life-saving” medicines being manufactured in rodent and pest infested laboratories, with mold growing on the walls, peeling paint and dirty equipment.

The “medicines” themselves pose a threat to patient health and safety because their contents are not regulated and they may contain none of the active pharmaceutical ingredient (API) to deliver the therapeutic benefit for which they were prescribed, the incorrect dosage or the wrong API. Patients are also placed at risk by the ingredients that counterfeiters use to produce their products: pesticides (boric acid); rat poison; leaded highway paint; commercial grade paint; cartridge ink; crayons; chalk, floor polish; brick dust; plaster and wallboard. There have also been reports of heavy metals, arsenic and even anti-freeze.

Counterfeiters, motivated by profit, are more concerned with the appearance of their products than the effect they might have on a patient. Due to advances in modern technology, the copies they are able to produce have become virtually indistinguishable from authentic tablets, and many can only be identified through detailed laboratory analysis.

Patients who unknowingly receive and ingest counterfeit medicines are denied the therapeutic benefit of the medicines prescribed by their physicians. When counterfeit medicines do not deliver the anticipated therapeutic benefit, not only are patients’ lives placed at risk, but they lose “confidence in medicines, healthcare providers and health systems” [1].

## **3. Industry efforts to mitigate the risk**

It is precisely because of the threat that counterfeit medicines pose to patients that pharmaceutical companies have implemented campaigns to detect, disrupt and deter major manufacturers and distributors of counterfeit medicines. In addition to our investigative efforts, we must:

- Incorporate anti-counterfeiting technologies into our products and packaging, making it more difficult for counterfeiters to copy our medicines, and easier for patients and healthcare providers to distinguish counterfeit from authentic medicines.

- Advocate for stronger penalties for individuals and/or organizations involved in the manufacture, distribution and sale of counterfeit medicines.
- Educate the public, healthcare professionals and policy-makers to the prevalence and dangers of counterfeit medicines.
- Forge partnerships with enforcement and regulatory authorities in which information on suspicious medicines is shared.
- Educate patients and healthcare professionals to the need to report suspicious medicines to the manufacturer.

To successfully stem the flow of counterfeit medicines, we must attack both supply and demand.

**On the supply side**, pharma companies should actively monitor their supply chains, including the pharmacies that dispense their medicines, to detect the presence of counterfeits. Concerns about the presence of counterfeit medicines should be pro-actively and thoroughly investigated, and the results referred to enforcement authorities for their action. Forging strong partnerships with enforcement authorities in each region and country is the keystone to a successful anti-counterfeiting program. Training those authorities not only raises their awareness to the counterfeiting problem, but also facilitates their ability to distinguish between counterfeit and authentic medicines.

**On the demand side**, we must continue efforts to educate patients by raising awareness to the threat that counterfeit medicines pose to their health and safety, supporting efforts by law enforcement and regulatory authorities, as well as NGOs and trade associations to raise awareness among patients to the threat that counterfeit medicines do pose to their health and safety.

### 3.1. Pfizer's anti-counterfeiting program

While the programs may vary from company to company, they have many common elements.

At Pfizer, for example, we conduct and manage pro-active investigations and refer the cases we develop to enforcement authorities for their action. Those investigations are initiated in response to “leads” from a variety of sources, including complaints from patients and healthcare professionals, observations by members of our sales force, information concerning changes in sales volume and patterns, from confidential informants, and from enforcement authorities. “Market surveys”, in which we make test purchases from pharmacies, are also undertaken as part of our program to monitor the integrity of our medicines sold in the legitimate supply chain.

Because we work our way up the hierarchy of the criminal enterprises we investigate, our referrals to authorities often identify the manufacturer or major distributor. Enforcement actions taken based on our referrals have a domino effect, protecting patients in the global market.

The success of our program can be attributed to our talent – colleagues placed strategically around the world with extensive law enforcement experience who know

how to initiate and develop cases – and the effective partnerships we have forged with enforcement authorities around the world.

Through these efforts, authorities around the world have taken significant enforcement actions, including the disruption of manufacturing and packaging operations, and counterfeiting networks distributing counterfeits to hospitals, pharmacies and other retail outlets

Pfizer's efforts to ensure the integrity of its medicines, is not limited to its robust anti-counterfeiting program, but extends to the incorporation of various security features into its packaging to make it more difficult for counterfeiters to make convincing copies of our medicines. These features vary from product to product and may include holograms, special paper and inks and tamper-resistant labels and closures to alert patients that a package has previously been opened.

### *3.2. Public-private collaboration mitigates threat to patient health and safety*

To mitigate the threat that counterfeit medicines pose to patients, Pfizer initiates pro-active investigations, the results of which are then referred to authorities for their action. These case studies are examples of the results that such collaborative efforts yield in our war against counterfeit medicines.

#### *3.2.1. Criminal enterprise targeting gulf states and the united states disrupted*

Based on referrals by Pfizer Global Security (GS), enforcement authorities in China and the United Arab Emirates (UAE) disrupted a major network, in the southern provinces of China, responsible for distributing large quantities of counterfeit medicines, manufactured in China, throughout the Gulf States and the United States (US).

Strands of this network were first discovered by GS in 2005. Through a well-coordinated effort by our three regional teams and GS Intelligence – including careful analysis of lab results, physical surveillance and shipping methodologies – we linked together what appeared on the surface to be separate investigations in China, Jordan, Romania, the UAE and the US.

The first blow to the criminal network was struck by authorities in the UAE in May 2010. Based on a referral from Global Security, authorities raided a hotel basement in which the counterfeits were stored and arrested an active police officer in Sharjah, described as the kingpin's right hand man. Although only counterfeit Viagra<sup>®</sup> was seized in those raids, our investigation linked the network to sales of counterfeit Dostinex<sup>®</sup> and Lipitor<sup>®</sup>, and the manufacture of Viagra<sup>®</sup>, Lipitor<sup>®</sup>, Xanax<sup>®</sup> and Aricept<sup>®</sup> in China.

Shortly after those raids, Global Security met with Chinese authorities, who accepted the case for criminal investigation. In May 2011, as a result of that referral, more than 300 Chinese law enforcement officers, from both the Public Service Bureau (PSB) and State Food and Drug Administration (SFDA), initiated enforcement

actions that dismantled one of the most prolific counterfeiting organizations ever uncovered in China. In two separate, but related enforcement operations on May 19 and May 21, PSB and SFDA raided two manufacturing sites and 26 storage facilities from which was seized as many as 200 million doses of counterfeit and unapproved generic medicines from at least five pharma companies. Also seized were large quantities of API, which may be beyond the capability of the authorities to accurately weigh. The seizures included equipment – 54 machines and 1,230 molds, tools and dies – with which to manufacture the counterfeits. Chinese authorities made 26 arrests, but a key member of the criminal enterprise, not present during the raids, evaded capture.

After the 2011 raids, we continued to monitor the target's travels and activities. We linked the target to the 2013 seizure of 1.2 million counterfeit Viagra<sup>®</sup> and Cialis<sup>®</sup> tablets in Saudi Arabia. When we located the target in Dubai, we launched an investigation that confirmed he was still distributing counterfeit Viagra<sup>®</sup>, and identified key locations of his ongoing operation. That information was shared with authorities, leading to his arrest, raids on three locations, and the seizure of 588,000 counterfeit Viagra<sup>®</sup> tablets (July 2014).

### 3.2.2. Criminal enterprise toppled, pharmacies and national lab shuttered

Rafael Brito, National Prosecutor for health-related matters, called it the biggest case ever developed in the Dominican Republic.

Simultaneous raids by Dominican authorities on 11 sites – including four pharmacies, where enforcement efforts were not a moment too soon. The counterfeit medicines had not only flooded the Dominican market, but posed a serious threat to US patients, as the network sought to introduce them into what they perceived as a very lucrative North American market. To evade detection by Customs and Border Protection Inspectors, they packaged counterfeit versions of Viagra<sup>®</sup> disguised as bottles of multi-vitamins. Among the premises raided was the clandestine laboratory where the counterfeits were packaged.

The raids, which culminated an investigation initiated by GS in early 2014 into the presence of counterfeit Ponstan<sup>®</sup> in the Dominican market, were made possible by the cooperation of the HSI (Homeland Security Investigations) Attaché, who provided access to the vetted National Police Unit.

### 3.2.3. Polish police pursue fleeing purveyor of counterfeit Viagra<sup>®</sup>

The arrest of a resident of Gorzow Wielkopolski culminated an investigation into a criminal network, based in Warsaw, for the distribution of counterfeit Viagra<sup>®</sup>. An investigator retained by Global Security first made contact in late 2015 and placed a small order, advising he wished to sample the quality of his product prior to placing a much larger order. The parcel arrived in early January, permitting GS to use payment collection from the Post Office to identify the seller's true name and bank account.

The investigator then placed an order for 1,200 Viagra<sup>®</sup>, which the suspect agreed to deliver in person on February 6. Shortly before the scheduled meeting, however,

he called the investigator and cancelled the meeting, stating he was too nervous for a face-to-face meeting as he had previously been convicted of and imprisoned for drug dealing.

Rather than meeting in person, he advised the investigator that he would mail the order in several packages between February 8 and 9. Police, who had been alerted to the scheduled face-to-face meeting were advised and established surveillance at the Post Office from which he had sent the first package. On February 9, police observed the suspect nearing the front door of the post office. They approached and identified themselves, but he evaded their grasp. Police gave chase and, after a brief struggle, apprehended him. The bag, which he had discarded during his escape attempt, was recovered. Inside the bag were three envelopes, one of which contained 200 Viagra<sup>®</sup> tablets intended for the investigator.

According to police, the suspect has been involved in the sale of counterfeit erectile dysfunction products for a long time. During the last four months alone, he had mailed several thousand counterfeit Viagra<sup>®</sup> tablets to customers. Nor was the sale of counterfeit medicines his only involvement in the trafficking of illegal substances. Police confirmed that he was previously convicted of illegal sale of various illegal drugs. A post-arrest search of his apartment revealed that he was illegally cultivating marijuana.

### 3.3. The online threat

Despite increased reports of breaches in legitimate supply chains, the Internet and the many professional looking websites that promise safe, approved, branded medicines from countries such as Canada or the United Kingdom (UK) also pose a major threat to patients.

Unsuspecting patients are easily lured by the ease with which they can order their medicines online, often without the need to consult a doctor or provide a valid prescription. While buying online, patients face a complete lack of transparency as to the true location of the “pharmacy” and the source and authenticity of the medicines it dispenses. Based on the “virtual” nature of the online sales of counterfeit medicines, it is difficult to determine the true physical location of any particular site. Many sites do not list a physical address; those that do frequently provide a false address, selecting a “trusted” market such as Canada.

Patients are at the greatest risk when they purchase their medicines from online pharmacies (OLPs) that are not licensed by, or registered with, their local regulatory authorities, many of which disguise their true location and mislead patients as to the source of the medicines they dispense.

It is possible for US patients to buy their medicines safely online through pharmacies that have been accredited by the National Association of Boards of Pharmacies (NABP) as complying with licensing and inspection requirements. Those pharmacies, designated as verified internet pharmacy practice sites (VIPPS), represent only a small percentage of online pharmacies. In a report issued in April 2016, the NABP found that, of the more than 10,000 websites it analyzed:

- 6,576 (61.5%) had no location posted on website
- 9,453 (88.5%) did not require a valid prescription
- 5,370 (50.3%) offered foreign or non-FDA approved medicines
- 1,318 (12.3%) dispensed controlled substances

9,605 (89.9%) appear to have affiliations with rogue networks of Internet drug outlets [2]. In addition to OLPs, counterfeit medicines are also readily available through Business to Business (B2B) platforms, social networking sites and bulletin boards.

Social networking sites are an attractive marketing platform, permitting distributors to market their products directly to consumers, providing anonymity and global reach to potentially billions of users with limited monitoring of user activity. For example, although the sale of medicine via Facebook is a violation of its terms and conditions, advertisements increasingly involve illicit products, including illegal, counterfeit or unauthorized medicines for the treatment of cancer, cardiovascular disease, panic and anxiety disorders, erectile dysfunction, and pain and inflammation. Intentional misspellings of product names or keywords, such as pharmacist or supplier, and the posting of images rather than text make it more difficult to search and locate sellers.

Bulletin boards also expose unsuspecting patients to the threat of counterfeit medicines. In many instances those bulletin boards who offer small quantities direct to patients also serve as drop shippers, fulfilling orders placed with OLPs or B2Bs. And in developing markets such as Latin America and Southeast Asia, sellers use popular microblogging sites to facilitate in-person transactions. Unlike the profiles found on some social networking sites, these microblogs appear to offer fewer choices and only target a specific therapeutic area.

### 3.4. Mitigating the online threat

To protect unsuspecting patients from the risk of obtaining counterfeit medicines online, many pharma companies have internet monitoring programs that include OLPs, social media sites and bulletin boards. These programs:

- Monitor OLPs and social media platforms to identify advertisements offering suspect medicines for sale
- Confirm, through test purchase and testing, whether counterfeits are being dispensed
- Identify the sellers
- Refer to law enforcement

Illegal OLPs that dispense counterfeit and generic medicines use call centers to contact patients on their behalf. While a call center may be located in any country, those selling medicines frequently misrepresent to patients that they are based in Canada, creating a false sense of confidence that the medicines they order, although cheaper than available from their brick and mortar pharmacies, are safe and effective. Disrupting such call centers is an effective way to disrupt the flow of counterfeit medicines to unsuspecting patients.

#### 4. A global threat

Many patients, particularly those in more developed countries with strong regulatory systems, would like to view counterfeiting as a myth, or a problem limited to less developed nations. Unfortunately, this is not the case. Counterfeit medicines are a problem from which no country, pharmaceutical company or therapeutic area is immune.

As noted by the WHO, “they can be found in illegal street markets, via unregulated websites through to pharmacies, clinics and hospitals” [3].

We have seen the spread of counterfeit medicines from developing countries with poor regulatory systems to countries such as Canada, the United States and the UK.

Counterfeit medicines are frequently smuggled into a country by those who either conceal them in electronic equipment, stuffed animals, or in false compartments constructed in shipping containers or even gas tanks of their vehicles.

We have noted that those involved in the distribution of counterfeits use complex transport routes in order to evade customs controls by disguising the true source of their product. In many instances, attempts are made to create an aura of legitimacy by passing shipments through countries such as the UK, Belgium, France, Canada and the US. Frequently, shipments are routed through Free Trade Zones, such as those found in the Middle East and Latin America, where they receive little if any scrutiny.

##### 4.1. Avastin<sup>®</sup> case: A clear example of the circulatory routing of counterfeit medicines

On February 12, 2012, the US Food and Drug administration (FDA) issued a public warning that counterfeit versions of the injectable cancer medication Avastin<sup>®</sup>, had been found in the US drug supply chain. On analysis, the fake contained cornstarch, acetone and other chemicals but no API originally detected in the clinical setting. Since that time, a second warning was issued on counterfeits that appear to be diverted, namely Turkish versions of Avastin<sup>®</sup>, Altuzan<sup>®</sup>. More than 130 doctors in 28 US states have been sent FDA warning letters concerning their dealings with the foreign supplier that was the source of the counterfeit Avastin<sup>®</sup>. Counterfeit Avastin<sup>®</sup> traveled to the US via Turkey, Switzerland, Denmark, the UK before reaching the US where it was purchased from a little-known drug wholesaler, Montana Healthcare Solution connected to online pharmacy Canadadrugs.com.

##### 4.2. The scope of the threat

The exact size of the counterfeiting problem is not known. Due to the criminal nature of their activities, counterfeiters seek to avoid detection, concealing the extent of the crimes committed, which makes data collection and reporting extremely difficult. One measure we have – the number of seizures reported by enforcement authorities around the world – represents only the tip of the iceberg.



In an article published in April 2015, in the American Journal of Tropical Medicines and Hygiene, authors assessed “counterfeit reports involving the legitimate supply chain using 2009–2011 data from the Pharmaceutical Security Institute Counterfeit Incident System (PSI CIS) database that uses both open and nonpublic data sources. Of the 1,510 identified CIS reports involving counterfeits, 27.6% reported China as the source country of the incident/detection. Further, 51.3% of the reports were counterfeit but the specific counterfeit subcategory was not known or verifiable. The most prevalent therapeutic category was anti-infectives (21.1%) with most reports originating from health-related government agencies. Geographically, Asian and Latin American regions and, economically, middle-income markets were most represented. A total of 127 (64.8%) of a total of 196 countries had no legitimate supply chain CIS counterfeit reports. Improvements in surveillance, including detection of security breaches, data collection, analysis, and dissemination are urgently needed to address public health needs to combat the global counterfeit medicines trade” [4]. Key findings of this review are depicted below.

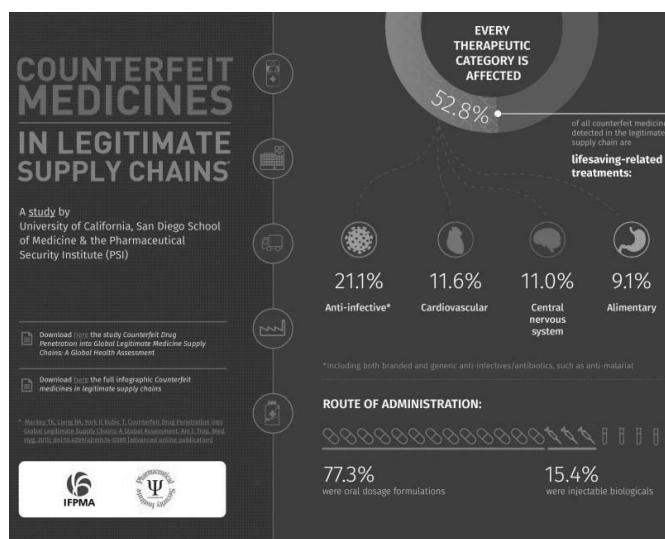
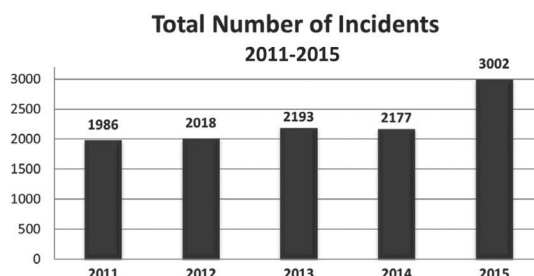


Fig. 1. Counterfeit medicines in legitimate supply chain.

## 5. The pharmaceutical security institute incident trends

Despite those limitations, the industry has continued to strive for improved data regarding counterfeit medicines. The Pharmaceutical Security Institute (PSI)<sup>2</sup> is a

<sup>2</sup>The Pharmaceutical Security Institute, founded in 2002, is a not-for-profit, membership organization dedicated to: Protecting the Public Health; Sharing Information on the Counterfeiting of Pharmaceuticals; and Initiating Enforcement Actions through the Appropriate Authorities. See [www.psi-inc.org](http://www.psi-inc.org).



non-profit organization composed of the security departments of thirty-three major pharmaceutical companies.<sup>3</sup> These companies share information on illegal manufacture and trade in pharmaceuticals. Because criminals who make and traffic illegal drugs target a wide range of companies' products, cooperation and data sharing among companies adds depth to their collective understanding of the problem [5].

While most of its efforts are in support of law enforcement and drug regulators, the PSI updates the public section of its website based on its annual report on the global pharmaceutical crime situation. The institute maintains a secure database, the Counterfeit Incident System (CIS) to which members report cases of fraudulent manufacture and mislabel of drugs, as well as cases of fraudulent packaging. The database is organized into incidents, discrete event[s] triggered by the discovery of counterfeit, illegally diverted or stolen pharmaceuticals. A unique tracking number links every incident to a distinct date, time, place, and product. Incidents can vary in size: sometimes small amounts of a single product are affected, other times large quantities of many products. Some incidents last for years, others are resolved in one year [5]. In the May 2016 report, *Illicit Trade – Converging Criminal Networks*, the OECD found that the PSI data is “perhaps the best counterfeiting data in the world”.

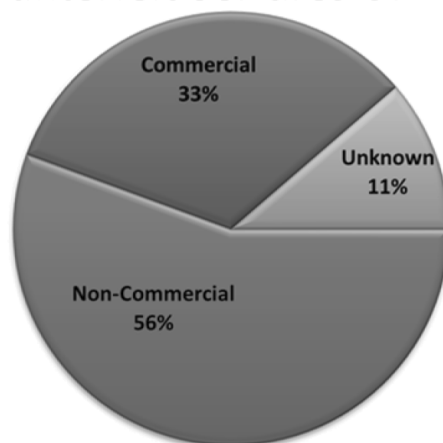
PSI defines a counterfeit incident as “the discovery of a medicine (whether branded or generic), which was deliberately and fraudulently produced and/or mislabeled with respect to identity and/or source to make it appear to be a genuine product.” [6] For reporting purposes, an authentic medicine that has been repackaged in counterfeit packaging is deemed a counterfeit incident [6].

This section and the ensuing materials are derived from PSI's recently updated website. PSI has collected data on counterfeiting, illegal diversion and theft incidents for the past fourteen years. The yearly totals for the last five years are shown in the below bar chart.

The Institute documented 3,002 incidents of pharmaceutical crime during 2015. This represented a significant increase from 2014 and an all-time annual high. From 2011 to 2015, total incidents increased by fifty-one percent (+51%).

<sup>3</sup>Abbott, Abbvie, Actavis, Amgen, Astellas, Astra Zeneca, Biogen, Boehringer Ingelheim, BMS, Chugai Pharmaceutical, Celgene, Eisai, Eli Lilly, Genentech, Gilead, GSK, Lundbeck, Roche, Horizon Pharma, Johnson and Johnson, Merck & Co, Merck KGaA, Mylan, Novartis, Novo Nordisk, Otsuka Pharmaceutical, Pfizer, Purdue Pharma, Sanofi, Servier, Sumitomo Dainippon, Takeda, Teva.

## Counterfeit Seizures 2015



To better understand the magnitude of the counterfeiting incidents in 2015, PSI continued to track the quantity of drugs seized in each law enforcement action. Any incident which involved the seizure of more than 1,000 dosage units was classified as a commercial incident. Those incidents involving less than 1,000 dosage units were classified as non-commercial. In 2015 there were 971 counterfeiting incidents which involved either customs seizures or police/health inspector raids. This represents a thirty-four percent (34%) increase over the prior year.

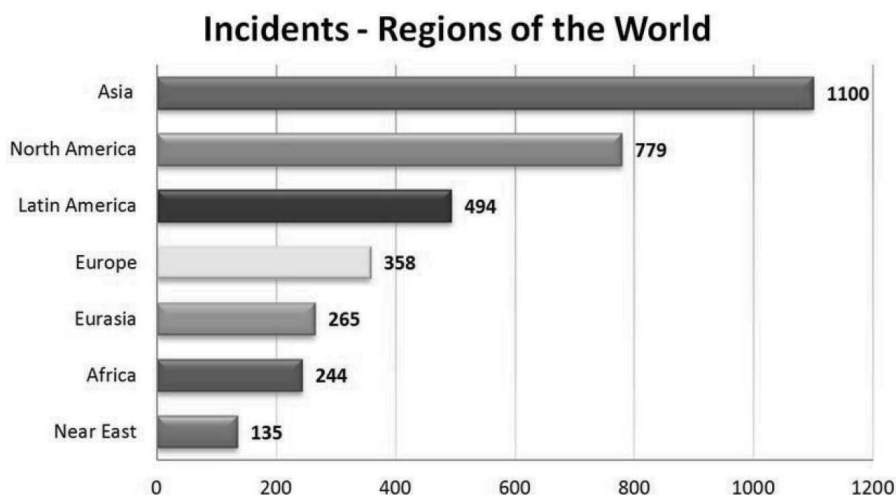
As the adjacent pie-chart shows, thirty-three percent (33%) of counterfeit medicines seizures made by law enforcement were of “commercial” size. Also, the number of non-commercial seizures increased significantly in 2015. The seizure of one thousand dosage units or less represented fifty-six percent (56%) of the total.

### 5.1. Geographic distribution

In 2015, incident data was analyzed with respect to seven regions of the world. As mentioned above, the PSI recorded a total of 3,002 pharmaceutical crime incidents. Every region experienced a pharmaceutical crime incident. In total, there were 128 countries found to have been impacted by pharmaceutical crime. A country is viewed as being impacted if the suspect medicines originated in that country, transited that country or were found in that country.

PSI documented a thirty-eight percent increase (+38%) in the worldwide incident total compared to the previous year. Incidents impacting the Asia Pacific region surpassed one thousand incidents annually for the first time in 2015. Also, incidents in North America increased over 100% from the previous year.

In the below chart, the regions are ranked in order from those experiencing the highest number of incidents to those with the lowest number of incidents.



Totals exceed 3,002 incidents because a region is included if it is the “origin, point of seizure or transit, or destination” of illegal pharmaceuticals.

It is important to note that the regions that are more frequently linked to incidents are not necessarily those with weak enforcement and inspection programs. Rather, countries in these regions are effectively identifying pharmaceutical crime through law enforcement activity and inspections by drug regulatory agencies. Many countries in regions with high incident totals are quite transparent in government operations and their activities are known to the media and public.

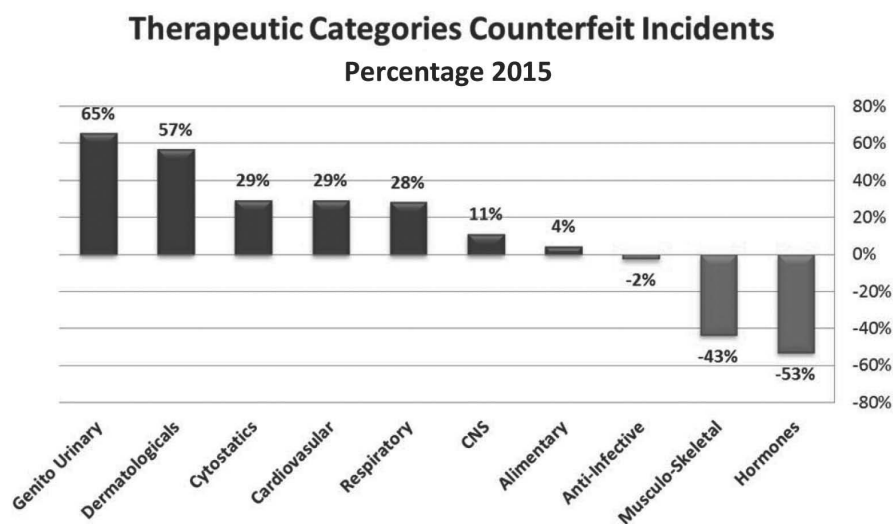
Those regions with seemingly low incident totals are not necessarily unaffected by or at a lower risk of pharmaceutical crime. Due to competing law enforcement priorities, lack of funding or inadequate regulatory structures, in certain regions of the world, counterfeit medicines often go undetected. It is important to recognize these facts, since they complicate region to region comparisons.

### 5.2. Therapeutic categories

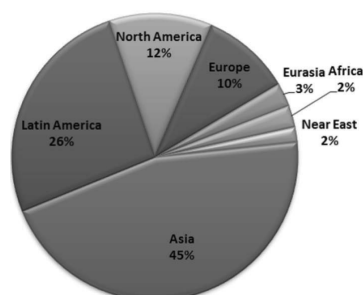
The 3,002 incidents occurring in 2015 involved 1,095 different pharmaceutical products. The number of products found in a single incident ranged from one drug to thirty-seven different drugs. Once again, pharmaceuticals in every therapeutic category were copied by criminal organizations.

CIS data revealed that medicines in the genito-urinary, anti-infectives and central nervous system (CNS) therapeutic categories contained the largest number of counterfeit incidents. These three categories were seen as having drugs which were the most frequently targeted by individuals engaged in pharmaceutical counterfeiting.

While the ranking of the top therapeutic categories were relatively unchanged, the Institute has noted seven therapeutic categories that have had a percentage increase on a year-to-year basis.



**Arrests by Region  
2015**



Specifically, the genito-urinary therapeutic category led with the largest percentage increase at sixty-five percent (+65%). Categories with percentage increases also included dermatologicals (+57%), cytostatics (+29%), cardiovascular (+29%), respiratory (+28%), CNS (+11%), and alimentary (+4%).

### 5.3. Enforcement efforts – Arrests

Arrests are often viewed as a key measure of law enforcement's effectiveness in addressing crime. However, law enforcement practices with regard to arrests can differ significantly from country to country. In addition to identifying law enforcement's involvement in a particular incident, PSI has been collecting information concerning arrests as an indicator of governments' commitment to address pharmaceutical crime.

Through member and open source reports, PSI documented the arrest of 1,375 persons involved in counterfeiting, diversion or theft of pharmaceutical drugs worldwide during 2015. This represented a decrease of eight percent (−8%) from the global arrests in 2014.

Not totally unexpected, the arrests in 2015 tracked fairly well with the incident data. So, the Asia region, with the highest number of incidents, also had the largest percentage of arrests.

## 6. Conclusion: What more can we do?

We have seen progress in the fight against counterfeit medicines, but much more needs to be done. Pharmaceutical counterfeiting is a high profit criminal activity that carries a low risk to the criminal which is why it has attracted drug traffickers, firearm smugglers and even terrorists. Those who counterfeit medicines seem confident that even if they get caught, they will get a mere “slap on the wrist”.

We must create a more favorable **enforcement environment through several steps:**

- Encourage policy-makers to recognize pharmaceutical counterfeiting as a serious crime with penalties commensurate with the threat that such conduct poses to patients around the world as well as the potential profits to be realized.
- Encourage authorities to make more resources available to enforce existing laws against pharmaceutical counterfeiting.
- Address the serious threat posed by rogue online pharmacies, seeking expedited procedures to shut them down, working in cooperation with internet service providers to block the flow of traffic to those sites and with credit card companies to prevent the processing of payments.
- Encourage collaboration within and between countries.
- Engage all key stakeholders in the fight against counterfeit medicines.

We must **educate and empower** patients to avoid counterfeit medicines in several ways:

- Raise awareness of the threat that counterfeit medicines pose.
- Buy from reliable sources.
- Notify healthcare professionals if they notice any difference in the appearance of the packaging, or the appearance and taste of, or responses or reactions to, their medicines.

Effective communications remain central to dispelling the myths surrounding counterfeit medicines, such as “counterfeiters only target lifestyle products”, or, “if a counterfeit contains some API it must be doing the patient some good”. As this article illustrates, it is impossible to know which medicines and patients will be targeted by counterfeiters. All counterfeit medicines can pose a risk, not only for what ingredients they do contain, but for what they don’t contain, and how they have been manufactured.

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## The global response to the threat of antimicrobial resistance and the important role of vaccines

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Antimicrobial resistance (AMR) has emerged as a significant threat to global health security and threatens the achievements of modern medicine. Research and successful development of new antibiotics, especially those with novel mechanisms of action vital to combat resistance, has slowed dramatically since the 1980s. Surveillance for AMR is highly variable globally with significant limitations in many countries impeding the ability to fully characterize the problem. Global efforts to control tuberculosis, malaria and HIV are facing increasing difficulties from the emergence of resistance. Similarly, bacteria causing some of the most common infections in communities or in hospitals such as *Escherichia coli* and *Klebsiella pneumoniae* have shown high levels of resistance to third generation cephalosporins requiring treatment with expensive carbapenems as last-resort. Additionally, *Streptococcus pneumoniae* has shown reduced susceptibility to penicillin in many regions, exceeding 50% in some settings. The cost in lives from AMR over the next 40 years could go as high as 10 million per year with the cost to economic development as high as \$3 trillion per year if current trends continue. In addition to ensuring appropriate use of antibiotics and development of novel classes with new or enhanced mechanisms of action, many plans for the global response call for new vaccines as integral to the fight against AMR. Vaccines and antibiotics should be used together to produce synergistic gains in public health, and ultimately, vaccines will extend the clinical utility of antibiotics. The decrease in cases of invasive pneumococcal disease and decrease in prescriptions for antibiotics in some settings resulting from the introduction of broad access to, and utilization of conjugate vaccines for *Streptococcus pneumoniae* exemplifies the synergy that can be achieved in the fight against AMR.

Keywords: Antimicrobial resistance (AMR), antibiotics, antibiotic stewardship, antibiotic surveillance, vaccines, pneumococcus, *S. pneumoniae*, pharmaceutical industry, conjugated vaccines, Haemophilus influenzae

### 1. Background

Antimicrobial resistance (AMR) has emerged as a significant threat to global health security [1,2]. The problem is so serious that it threatens the achievements of modern medicine and a post-antibiotic era – in which common infections and minor injuries can kill – is a very real possibility for this century. Furthermore, the hard-won gains made in health and development, in particular those brought about

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through the health-related Millennium Development Goals, are put at risk by increasing AMR and the sustainability of the public health response to many communicable diseases, including tuberculosis, malaria and HIV/AIDS is jeopardized [3].

AMR develops when a microorganism (bacteria, virus, parasite and fungus) no longer responds to a drug to which it was originally sensitive. Drugs for treating infections lose their effect because the microbes change; either they mutate or acquire genetic information from other microbes to develop resistance. The phenomenon is accelerated by use, and especially misuse, of antimicrobial medicines whereby resistant strains survive and aggregate. The problem can be further amplified when antimicrobial agents of substandard or falsified quality are procured and used by patients [4]. The situation translates into standard treatments no longer working – infections are harder or impossible to control; the risk of the spread of infection to others is increased; illness and hospital stays are prolonged, with huge added economic and social costs [5]. By extension, the risk of death is greater – in some cases twice that of patients who have infections caused by non-resistant bacteria [6].

To make matters worse, the research and successful development of new antibiotics, especially those with novel mechanisms of action vital to combat resistance, has slowed dramatically since the 1980s [7,8]. For example, the number of antimicrobial agents approved by the FDA steadily dropped from 16 for the period 1983–1987 down to three for the period 2008–2012. Though the number of approvals has increased somewhat since 2012, most of all antibiotics approved for use in patients today are derived from a limited number of types, or classes, of antibiotics that were discovered by the mid-1980s [9].

The lack of development of new classes of antibiotics is even more concerning than the decline of drug approvals because resistance to one antibiotic often leads to resistance to multiple antibiotics within the same class. Many factors have contributed to this decline, but it is primarily economic factors and regulatory constraints, including the rethinking of statistical principles of non-inferiority trial designs in the 1990s, which disproportionately has affected trials for antibacterial development [10].

## **2. Current global burden of AMR**

In assessing the magnitude of AMR globally, the quality and capacity for surveillance and the available information is highly variable across countries and regions. Similarly, it is quite variable within the realm of infectious disease, with surveillance for resistance being more advanced for diseases like tuberculosis (TB) and malaria managed more as public health programs compared to resistance among bacteria that cause common healthcare associated and community-acquired infections [11]. In response, the World Health Organization (WHO) has taken important steps to characterize and measure the global magnitude of AMR with special emphasis on

antibacterial resistance (ABR) to complement long-established surveillance efforts in TB and malaria and more recent efforts for HIV.

With respect to TB, malaria, and HIV, surveillance data demonstrate alarming trends related to AMR. For example, multidrug resistant TB (MDR-TB) is a growing problem and largely under-reported with the strong potential to compromise global control of TB; in settings such as India, patients with totally drug resistant TB have even been identified [12,13]. Related to malaria, foci of artemisinin resistance have been identified in multiple countries in Southeast Asia; further spread or emergence in other regions of this resistance could jeopardize important gains in malaria control made since 2000 [14]. Finally, increasing levels of transmitted anti-HIV drug resistance have been detected among patients starting antiretroviral treatment in low- and middle-income countries; available data suggest that 10%–17% of patients without prior history of ART in high income countries are infected with virus resistant to at least one antiretroviral drug [15–18].

With respect to the magnitude of ABR, for its first global report in 2014, WHO obtained information on resistance to antibacterial drugs commonly used to treat infections from more than 100 member states of the United Nations (UN) [19]. For this exercise, many gaps in information on pathogens of major public health importance, including gaps in surveillance, and a lack of standards for methodology, data sharing and coordination were identified. Nonetheless this was an important step forward on measuring the burden of ABR. As an overall finding of great concern, very high rates of resistance ( $\geq 50\%$ ) have been observed in bacteria that cause common healthcare associated and community-acquired infections (e.g. urinary tract infection, pneumonia) in all of the WHO regions.

More specifically, the assessment focused on resistance in seven bacteria of international concern causing some of the most common infections in different settings such as the community, in hospitals or transmitted through the food chain including *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Nontyphoidal salmonella*, *Shigella species*, *Neisseria gonorrhoea* [20]. The main findings regarding antibacterial resistance from the WHO surveillance project from 2014 are included in Table 1. Of note, oral treatment options for urinary tract infections acquired in the community are becoming more limited. Additionally, expensive and more toxic second-line drugs requiring additional expensive monitoring are increasingly being required to effectively treat patients for a variety of infections and these drugs are often not widely available in many resource limited settings. Finally, resistance to drugs of last resort for some infections such as *Neisseria gonorrhoea* has been widely detected globally.

Finally, WHO has identified that major gaps exist in surveillance and data sharing related to the emergence of antibacterial resistance in foodborne bacteria and its potential impact on both animal and human health. Surveillance is hampered by insufficient implementation of harmonized global standards. The multi-sector approach needed to contain antibacterial resistance includes improved integrated surveillance of resistance in bacteria carried by food-producing animals and in the food chain, and

Table 1

Summary of findings from WHO's *Antimicrobial resistance: Global report on surveillance 2014* focused on seven bacteria of international concern causing common infections [95]<sup>†</sup>

Bacterial agent	Finding	Implication
<i>Escherichia coli</i>	– High % of resistance to 3 <sup>rd</sup> generation cephalosporins	– Treatment of severe infections in many settings must rely on expensive carbapenems as last-resort – Limited options for oral agents to treat community acquired infections (UTIs)
<i>Klebsiella pneumoniae</i>	– High % of resistance to 3 <sup>rd</sup> generation cephalosporins – Resistant to carbapenems in most countries; resistance up to 54% in some settings	– Treatment of severe infections in many settings must rely on expensive carbapenems as last-resort
<i>Staphylococcus aureus</i>	– High rates of methicillin-resistant (MRSA) among patients with severe skin and wound infections	– Expensive 2 <sup>nd</sup> -line drugs needed for treatment with need to monitor for severe side-effects – Standard prophylaxis with 1 <sup>st</sup> -line drugs for orthopaedic and other surgical procedures with limited effect
<i>Streptococcus pneumoniae</i>	– Reduced susceptibility to penicillin detected in all WHO regions; exceeded 50% in some reports – Limited comparability of laboratory standards and variation in how reduced susceptibility is reported	– Extent of problem and impact on patients not clear given laboratory issues – Because invasive disease (e.g. pneumonia and meningitis) is common and serious in children and elderly, better monitoring of resistance is urgently needed
Nontyphoidal salmonella (NTS) and shigella species	– Fluroquinolone resistance comparatively lower than in <i>Escherichia coli</i>	– Some reports of high resistance in NTS of great concern because resistant strains associated with worse patient outcomes
<i>Neisseria gonorrhoea</i>	– Decreased susceptibility to third-generation cephalosporins (last resort treatment) verified in 36 countries and growing problem	– Potential for global untreatable venereal disease

<sup>†</sup>Information compiled from WHO AMR Report, 2014 – World Health Organization (2014) Antimicrobial resistance: global report on surveillance 2014. <http://www.who.int/drugresistance/documents/surveil-lancereport/en/>.

prompt sharing of data. Integrated surveillance systems would enable comparison of data from food-producing animals, food products and humans [21].

### 3. Global economic impact of AMR

Antibiotic-resistant infections add considerable and avoidable costs to the already over-burdened healthcare systems. In most cases, antibiotic-resistant infections re-

Table 2  
Estimated annual costs from AMR in three regions [96]<sup>‡</sup>

	EU	Thailand	US
Population	500 million	70 million	310 million
People infected with bacteria with AMR	–	–	~ 2,000,000
Deaths/year from AMR	25,000	> 38,000	> 23,000
Added morbidity from AMR	2.5 million extra hospital days	> 3.2 million hospital days	> 2.0 million illnesses
Overall societal costs	– € 900 million, hosp. days – Approx. € 1.5 billion per year	– \$84.6–202.8 million, direct – \$1.3 billion, indirect	– Up to \$20 billion direct – Up to \$35 billion indirect
Source	ECDC 2007 [97]	Pumart et al. 2012 [98]	CDC, 2013 [99]

<sup>‡</sup>Information compiled from WHO AMR Report, 2014 – World Health Organization (2014) Antimicrobial resistance: global report on surveillance 2014. <http://www.who.int/drugresistance/documents/surveillance-report/en/> and slide deck on report provided in public domain by WHO.

quire prolonged and costlier treatments, extended hospital stays, and additional doctor visits and healthcare use resulting in greater disability and death compared with infections that are easily treatable with antibiotics.

Sources available from some countries help to illustrate the current situation in terms of the economic impact of AMR as a baseline for gauging what the future might hold (see Table 2). In the European Union (EU) alone, the additional burden posed by resistance every year, focusing only on a limited group of healthcare-associated bacterial infections, is in the range of 2.5 million hospital days, 25,000 deaths and economic losses on the order of €1.5 billion due to extra healthcare costs and productivity losses [22]. According to a recent study in Thailand, in 2010 antimicrobial resistance was responsible for at least 3.2 million extra hospitalization days and 38,481 deaths, and for losses amounting to \$84.6–\$202.8 million in direct medical costs and more than \$1.3 billion in indirect costs [23]. In the United States (US), where approximately 23,000 people die each year as a direct result of AMR, estimates for the total economic cost of antibiotic resistance vary but have ranged as high as \$20 billion in excess direct healthcare costs, with additional costs from lost productivity as high as \$35 billion a year (2008 dollars) [24–26].

From the global perspective, the Independent Review on AMR commissioned by the Government of the United Kingdom (UK) and led by the renowned economist Jim O’Neill commissioned a study in 2014 to estimate the global costs of AMR until 2050 in the absence of any progress in addressing the challenge [27]. The results from this analysis demonstrated that if current trends persist resulting in increasing morbidity and mortality related to AMR, the costs in terms of healthcare, loss of life, productivity, and by extension, global economic development are potentially staggering at orders of magnitude higher than seen at present and render AMR as an urgent public health crisis requiring immediate intervention [28].

From the commissioned analysis, based on various conservative assumptions, on average over a 40-year span, the world GDP loss runs between \$53 billion to \$3 trillion per year [29]. In some scenarios, up to 10 million lives per year could be lost by 2050 (up from 700,000 estimated deaths presently occurring worldwide) and a cumulative \$100 trillion of economic output are at risk due to the rise of drug-resistant infections if proactive solutions are not put into place now to slow down the rise of drug resistance. As with all forecasts of this sort, it is possible that the analysis represents an overestimate of the scale of the problem; however, it is even more likely the analysis underestimates the potential future impact as the secondary effects of antibiotics losing their effectiveness were not even considered [30]. Additionally, new forms of resistance have already emerged much sooner than expected, such as the highly disturbing discovery of transferable colistin resistance, reported in late 2015 [31].

#### **4. The need for stewardship**

A major contributor to the emergence of AMR has been poor management over time of the use of existing antimicrobial agents. The problem is pervasive in both developed countries and those of constrained resources. Demand for these agents is poorly managed. Large quantities of antimicrobials are used globally on patients who do not need them, while others who need them do not have access. Antibiotic prescriptions are often not informed by up to date surveillance, and rapid diagnostic testing that could guide prescribing more effectively is limited in many settings.

Some research from the US has shown that as much as 50% of the time antibiotics are prescribed when they are not needed or they are misused which promotes antibiotic resistance [32]. In European countries, systemic antibiotics are prescribed in greatest volume to ambulatory patients, mostly for respiratory tract infections [33]. Recent studies from Eastern Europe have identified the inappropriate use of antibiotics for viral infections of the respiratory tract and sub-therapeutic dosing as common in both hospital and ambulatory settings (in one published report correct dosing was reported in 38% of outpatient and 74% of medical charts of children with respiratory infections in hospital that were reviewed) [34,35] In Thailand, unnecessary use of antibiotics is seen among both health professionals and the public [36–38] One study in a tertiary care hospital revealed that only 7.9% of the upper respiratory tract infections (URIs) in the facility were caused by bacteria [39,40] Despite this, in Thailand most URIs are treated with antibiotics by hospitals, health centers, drug stores and patients themselves [41–45]. Liberal use of antibiotics endangers the health of patients without observable clinical benefits, since it neither reduces the rate of complications nor quickens recovery when the illness is caused by a virus [46,47]. Finally, the full extent of the wide usage of antibiotics in agriculture is unknown due to a lack of surveillance, and antibiotics that are vital for human health are not restricted from usage in animals.

## 5. Examples of stewardship

Increasing awareness of antimicrobial resistance and promoting the rational use of antibiotics among prescribers and the general public are key to combating the unnecessary use of these drugs [48,49]. Antibiotics are a limited resource. The more that antibiotics are used today, the less likely they will still be effective in the future. Therefore, doctors and other healthcare professionals around the world are increasingly adopting the principles of responsible antibiotic use, often called antibiotic stewardship. Stewardship is a commitment to always use antibiotics only when they are necessary to treat, and in some cases prevent, disease; to choose the right antibiotics; and to administer them in the right way in every case [50]. Effective stewardship ensures that every patient gets the maximum benefit from the antibiotics, avoids unnecessary harm from allergic reactions and side effects, and helps preserve the life-saving potential of these drugs for the future. Efforts to improve the responsible use of antibiotics have not only demonstrated these benefits but have also been shown to improve outcomes and save healthcare facilities money in pharmacy costs.

One global example of antibiotic stewardship that is working well is the Green Light Committee (GLC) Initiative undertaken to combat the growing epidemic of MDR-TB [51]. The initiative was established as a public-private partnership nearly 20 years ago by WHO in response to difficulties experienced by countries in finding and funding stable supplies of high-quality anti-TB drugs and to address the growing emergence of resistance resulting from poor quality drugs being used in many countries. The goal was to promote access to and rational use of second-line anti-TB drugs for the treatment of MDR-TB. Stakeholders included academic institutions, civil society organizations, bilateral donors, Governments, and the private sector. The effectiveness of the partnership emerged in part from its ability to link access, rational use, technical assistance, and policy development. Data from research design to evaluate the mechanism and its guiding principles demonstrate the impact and effectiveness of the initiative since its launch. In one large multinational prospective cohort study evaluating treatment approaches and comparing outcomes for MDR-TB patients in countries using the GLC mechanism versus those that did not showed that treatment success among patients in countries using the mechanism was substantially greater [83% versus 60%, respectively; ( $p < 0.001$ )] and by extension the initiative was shown to have reduced further emergence of anti-TB drug resistance [52]. The GLC mechanism may be useful in the development of other partnerships needed in the rational allocation of resources and tools for combating AMR more broadly.

Other examples at the country level of important stewardship programmes that have been launched in developed countries include “Strama” in Sweden [53]; the *Get Smart: know when antibiotics work* programme of the US Centers for Disease Control and Prevention [54], and several national public campaigns in Europe [55,56]. In the context of country settings of more limited resources, the Antibiotics Smart Use (ASU) program was introduced in Thailand in 2007 as an innovative model to

promote the rational use of medicines and counteract antimicrobial resistance building on interventions undertaken prior to 2007 that had only been partially successful and it is showing great promise [57].

## **6. Global response**

In 2014, the UK Prime Minister commissioned a wide reaching independent review [58], led by the internationally renowned economist Jim O'Neill and co-founded and hosted by the world's second largest medical research foundation, the Wellcome Trust, to explore the economic issues surrounding antimicrobial resistance. After 18 months of consultation, Jim O'Neill presented ten key elements to tackle AMR in a global way in May 2016 including public awareness, sanitation and hygiene, antibiotics in agriculture and the environment, vaccines and alternatives, surveillance, rapid diagnostics, human capital, new drugs, global innovation fund, and an international coalition for action [59].

In 2014, US President Barack Obama signed an Executive Order directing key Federal departments and agencies to take action to combat the rise of antibiotic-resistant bacteria [60]. The US Administration also released its National Strategy on Combating Antibiotic-Resistant Bacteria. In addition, the President's Council of Advisors on Science and Technology (PCAST) released a related report on Combating Antibiotic Resistance. In addition, the Biomedical Advanced Research and Development Authority (BARDA) established the Broad Spectrum Antimicrobials (BSA) Program in April 2010 to boost the development of novel antibacterial and antiviral drugs to treat or prevent diseases caused by biological threats [61].

In Europe, the Innovative Medicines Initiative's (IMI) public-private partnership model is based on a partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). In March 2012, IMI launched its first call for proposals under the 'New Drugs for Bad Bugs' (ND4BB) program, a major public-private partnership effort to address bottlenecks in the discovery and development of new antibiotics. [http://www.who.int/phi/implementation/1\\_infobrief\\_innovative\\_medicines\\_initiative\\_ND4BB\\_models\\_of\\_collaboration.pdf](http://www.who.int/phi/implementation/1_infobrief_innovative_medicines_initiative_ND4BB_models_of_collaboration.pdf) [62]. In October 2014, the ND4BB launched the DRIVE-AB Project. DRIVE-AB aims at developing options for novel economic models of antibiotic research and development (R&D) and responsible use of antibiotics.

In January 2016, a Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance called on governments to work with industry to develop new and alternative market structures that provide more dependable and sustainable market models for antibiotics, and to commit the funds needed to implement them [63]. The Declaration was signed by 100 pharmaceutical, biotech and diagnostics companies and 13 associations. It sets commitments to further action on drug resistance by its signatories, across three broad areas: reducing the development of drug resistance, increasing investment in R&D that meets global public health needs, and improving access to high-quality antibiotics for all.



In the last two years, AMR has gained prominence on the agenda of G7 leaders who have publically referred to this issue as one of the most important global threats. During the German presidency, AMR was mentioned in the leaders' declaration from Schloss Elmau summit in June 2015 [64] and the Berlin G7 Health Ministers declaration in October 2015 [65]. Germany's engagement on AMR was continued under the Japanese presidency with the launch in May 2016 of the G7 Ise-Shima Vision for Global Health [66], the vision is composed of four pillars:

1. Reinforcing the global health architecture to strengthen responses to public health emergencies.
2. Attaining UHC with strong health systems and better preparedness for public health emergencies.
3. AMR.
4. R&D and innovation.

Finally, for the first time, the G20 will discuss a health issue; the Chinese G20 summit which will be held in September 2016 will discuss global solutions to combat AMR.

## **7. WHO engagement**

On May 2015, the World Health Assembly (WHA) of the WHO endorsed the AMR Global Action Plan (GAP). The GAP is composed of five strategic objectives:

1. Objective 1: Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.
2. Objective 2: Strengthen the knowledge and evidence base through surveillance and research.
3. Objective 3: Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures.
4. Objective 4: Optimize the use of antimicrobial medicines in human and animal health.
5. Objective 5: Develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

The WHA also called Members States to develop their own national action plans based on the GAP and report on progress at the WHO WHA in May 2017. The WHO also released last April a worldwide country situation analysis on AMR which showed that only 34 out of 133 participating in the survey have a comprehensive national plan to fight resistance to antibiotics and other antimicrobial medicines. The situation varies sensitively depending on the region. After the adoption of the GAP, countries are now entering an "implementation phase": some countries are already well advanced in the development of their action plans, while others need support and guidance.

As a follow-up to the request made in resolution WHA68.7 [67], WHO is in the process of establishing a global development and stewardship framework to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions. The framework should also provide guidance to member states preserving existing antimicrobial medicines, and promote affordable access to existing and new antimicrobial medicines and diagnostic tools.

Finally, the UN Secretary General and the WHO Director General will co-host a High Level Meeting (HLM) on AMR in September 2016 in the margins of the UN General Assembly. The meeting aims at increasing political awareness, engagement and leadership on antimicrobial resistance.

With respect to the response to AMR by the private sector, in the Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance, pharmaceutical companies expressed the commitment to work to reduce the development of AMR through its support to continued education for clinical professionals on appropriate use and strengthened infection control via improved hygiene, vaccination, and preventive treatments and through measures to reduce environmental pollution from antibiotics, along with a 'one health' approach towards prudent and responsible use, including a global reduction of unnecessary antibiotic use in livestock.

## **8. Role of vaccines in the global fight against AMR**

In the face of the alarming trends in AMR and the projected economic impact, in addition to ensuring the appropriate use of antibiotics and the development of novel classes with new or enhanced mechanisms of action, vaccines are critical tools in the fight against infectious diseases and AMR. Vaccines can prevent infections and therefore lower the demand for therapeutic treatment with antimicrobials and, in turn, reduce disease with antimicrobial strains and also attenuate further increases in drug resistance. Vaccines protect the vaccinated individual by direct immunization and can protect others through indirect immunization (assuming the overall vaccination rate is high enough). Vaccines and antibiotics should be used as complementary tools to produce synergistic gains in public health. Ultimately, vaccines can extend the clinical utility of antibiotics by reducing infections and limiting their transmission, this impact in turn allows antimicrobials to be used more sparingly and under closer supervision. For example, a Finnish study found that the introduction of a pneumococcal vaccine covering more strains reduced antibiotic purchases by 8% [68].

Nevertheless, this positive synergy can be reversed if either component – vaccines or drugs – are not used well. When compliance with vaccine schedules is compromised and/or adherence to policy recommendations is rejected, optimal prevention of infection is not achieved, and infection rates may increase. As a result, more and more antimicrobials will need to be used. Even when the antimicrobials are used

carefully, emergence of resistant pathogens still occurs, but when they are used indiscriminately, as is too often the case, then the problem is made worse. From an investment standpoint, if vaccines are underutilized, there is less incentive to develop new ones; and if antimicrobials are over utilized, their effective commercial life becomes shorter and there is less incentive to develop replacements. Better public health policies to emphasize increased compliance with vaccine schedules and better stewardship of antibiotic drugs are essential. From a public health policy perspective, the recent focus on the failure of markets to ensure access, conservation, and innovation in the antimicrobial drug marketplace should be broadened to include incentives for vaccines that can help meet the end goal of reducing the need for antimicrobial treatment while making sure the drugs are effective when they are needed [69]. The role of national vaccination programs were reviewed in a recent study [70]. That study showed decreased antibiotic use associated with initiation of vaccination programs or increased uptake of available vaccines (e.g. influenza and pneumococcal vaccines). Reductions in antibiotic use ranged from 5 to 10% in randomized controlled trials, to a relative reduction of disease incidence of 64% in epidemiological studies. This suggests that vaccination programs may reduce antibiotic utilization and, consequently, antibiotic resistance.

## 9. Value of conjugated vaccine technologies

In the battle against evolving resistance, conjugate vaccine technology is especially valuable. This vaccine technology has enabled the production of several commercially and medically important vaccines (various capsule types of *Haemophilus Influenzae*, *N. meningitidis* and *Streptococcus pneumoniae*. The potential to add protection against additional strains (e.g. PV7 to PV13 in the case of *Streptococcus pneumoniae*) is ideally suited to the realities of infectious diseases. As additional antibiotic resistance strains emerge, conjugate technology will allow the development of new safe and protective vaccines against these strains.

There are several examples of available vaccines having a positive impact on preventing emergence of antibiotic resistance in targeted bacteria. Infections caused by the gram positive cocci *Streptococcus pneumoniae* are frequent causes of morbidity and mortality worldwide. Infections caused by *Streptococcus pneumoniae* include otitis media and sinusitis, as well as more severe invasive disease such as pneumonia, sepsis, and meningitis (invasive pneumococcal disease or IPD). The WHO estimates that more than 1.6 million people – including more than 800,000 children under five years old – die every year from pneumococcal infections [71]. This also includes elderly persons and those with underlying diseases who are also susceptible to severe infections caused by *Streptococcus pneumoniae* [72].

In the year 2000, pneumococcal conjugate vaccines (PCVs) were introduced in the US; they have since then been introduced in the national childhood vaccination programs in many countries worldwide. Since its introduction to US infants and

toddlers, heptavalent pneumococcal conjugate vaccine (PCV7), licensed in the US as a four-dose schedule (a three-dose primary series at two, four, and six months with a booster dose at 12–15 months, aptly named a “3 + 1 schedule”) [73], has virtually eliminated US childhood IPD caused by the seven pneumococcal serotypes contained in PCV7 [74]. The subsequent introduction of 13-valent PCV (PCV13) in 2010 added protection against an additional six pneumococcal serotypes that: 1) were not previously covered by PCV7; and 2) become increasingly prevalent after PCV7 was introduced [75].

Zhou et al. reported that the use of PCV7 against drug-resistant *Streptococcus pneumoniae* (DRSP) has led to a decrease in prescriptions for antibiotics, which is likely to lead to less antibiotic use [76]. This well-documented case suggests the role vaccines can play in decreasing antibiotic resistant infections. Additionally, Dagan et al reported that use of PCVs has led to the reduction of DRSP [77]. Whitney et al reported that the PCV not only reduces the incidence of invasive antibiotic-resistant pneumococcal infections in young children receiving the vaccine, but it also reduces transmission of these strains to their younger siblings and to adults [78]. Klugman et al. showed in a 2001 study that PCVs have shown a high degree of success in preventing pneumococcal bacteremia in children [79]. They also reduce the acquisition of carriage of vaccine serotypes in the nasopharynx, and reduce otitis media caused by those serotypes. Klugman also stated that PCVs interrupt the transmission of antibiotic-resistant pneumococci and thus decrease the burden of antibiotic resistance in immunized children and in their contacts. Kyaw et al reported in a 2006 study that the rate of antibiotic-resistant invasive pneumococcal infections decreased in young children and older persons after the introduction of the conjugate vaccine. While there was an increase in infections caused by serotypes not included in the vaccine, the net effect was a reduction in number of infections and lower use of antibiotics [80].

The first PCV (PCV7) was licensed in the US for use in infants and children in 2000. A recent US study showed that between 1998 and 2008, there were a 64% decrease in antibiotic-resistant pneumococci among children and a 45% decrease among adults over 65 [81]. Data from a South African study showed that since that country’s introduction of a PCV in 2009, in addition to the expected reduction in the overall incidence of invasive pneumococcal disease by about two-thirds in infants (the age group vaccinated) and in adults, there was also a reduction in penicillin-resistant infections in both vaccinated groups [82]. This is the first time such benefits have been observed outside the developed world.

Thus the evidence is mounting that vaccines can serve as an effective tool for reducing disease caused by drug-resistant strains as a complement to rational use of antibiotics. Unfortunately, continued widespread antibiotic use has resulted in an increase in disease by serotypes not covered by the PCV7 vaccine, such as serotype 19A, which has become the leading cause of the remaining invasive pneumococcal infection. The new PCV13 was approved in 2010 and was developed to provide

immunity against this and other serotypes not covered by PCV7. Thus, we must continue to rely on the effectiveness of existing and new antibiotics to control infections caused by the emergence of new strains not covered by existing vaccines.

PCV13 provides an opportunity to prevent even more resistant infections of pneumococcal disease. In a recent study done by the CDC an examination of the US *Streptococcus pneumoniae* isolates from 10 Active Bacterial Core Surveillance sites demonstrated a decrease of multidrug – resistance in the PCV13 covered strains [83]. The study specifically showed that there was a 93% and 86% reduction of isolates that were resistant to either single or multiple antibiotics, respectively. The study also showed an increase in antibiotic resistance for *Streptococcus pneumoniae* isolates that were not covered by the vaccine.

Strains of the gram negative bacillus *Haemophilus influenzae* are found as both respiratory tract commensals and respiratory and invasive pathogens. The major diseases caused by *Haemophilus influenzae* include childhood pneumonia, meningitis, and bacteremia, (primarily caused by type b strains), and community-acquired pneumonia (CAP) in adults, acute otitis media (AOM), acute sinusitis, and acute exacerbations of chronic bronchitis (AECB).

Prior to introduction of *Haemophilus influenzae* type b (Hib) vaccines in 1977, meningitis and pneumonia caused by Hib was responsible worldwide for roughly three million serious infections and 386,000 deaths per year. Furthermore almost 95% of these infections, and 98% of deaths, occurred in developing countries [84].

*Haemophilus influenzae* are known to contain resistance to several clinically relevant antibiotics including-lactam antibiotics, macrolides, ketolides, azalides, quinolones, tetracyclines, chloramphenicol, trimethoprim and sulfamethoxazole [85]. Widespread and systematic vaccination with the Hib vaccine has virtually eliminated Hib disease in most industrialized nations, and the Hib vaccine had been introduced in 192 countries by the end of 2014 [86].

With respect to the impact of Hib vaccination on antibiotic resistance, several studies have seen a positive correlation between use of the Hib vaccine and a reduction in resistance to one or more antibiotics. In a large 10-year Italian study, investigators demonstrated a marked 50% decrease in  $\beta$ -lactamase – mediated resistance to ampicillin and related  $\beta$ -lactam antibiotics [87]. Similarly, a Spanish study showed that antibiotic resistance in *Haemophilus influenzae* decreased in Spain from 1997 to 2007, due to a Hib vaccine – related reduction in the use of several antibiotics [88]. Citing one example from that study, while community consumption of trimethoprim-sulfamethoxazole decreased by 54%, resistance to those antibiotics decreased from 50 to 34.9% [89]. A US study also demonstrated a decrease in prevalence of  $\beta$ -lactamase producing respiratory tract isolates of *Haemophilus influenzae* in the US [90]. Finally, a longitudinal European surveillance study showed that the overall resistance of *Haemophilus influenzae* to amoxicillin in Europe to decline (1997/98 and 2002/03), due to a decreasing number of  $\beta$ -lactamase – producing strains [91].

In addition to the demonstrated, positive effects that bacterial vaccines have on reducing antibiotic resistance, a similar effect is seen with certain viral vaccines, especially in terms of secondary infections. For example in the case of primary viral influenza infections, we often see bacterial respiratory infections due to associated *Streptococcus pneumoniae* and *Haemophilus influenzae*, especially in the elderly. While it is within the scope of practice to prescribe antibiotics to treat these infections, prior immunization with the viral influenza vaccine can prevent secondary bacterial infections and thereby reduce the need for antibiotic usage. For example, in a Canadian study, the introduction of universal influenza vaccination, resulted in a 64% decrease in influenza associated respiratory disease antimicrobial prescriptions in the province of Ontario [92]. This effect has been corroborated by others [93].

In the case of varicella virus infection (chickenpox), secondary infection by *Staphylococcus aureus* is common and causes an estimated 150,000 infectious every year, each requiring the administration of antibiotics [94]. The same report also reported a 42.9% to 47.0% reduction in days of antibiotic use after influenza vaccination in healthy working adults. More widespread usage of the varicella vaccine would be expected to reduce secondary infections caused by *Staphylococcus aureus*, thus reducing the need for antibiotics administration against this often resistant pathogen.

## 10. Conclusions

AMR represent a major threat to global health security with the potential to have devastating effects on global economic development. If current trends in AMR continue unchecked, upwards of 10 million lives per year and trillions of dollars of losses to the global economy could occur annually by 2050. Surveillance that generates reliable data is the essential basis of sound global strategies and public health actions to contain AMR, and is urgently needed around the world. Furthermore, the supply of new anti-microbial agents is insufficient to keep up with the increase in drug resistance as older agents are used more widely and non-judiciously and microbes further evolve to resist them. As no truly new class of antibiotics has been developed for decades, new drugs to replace the ones that are not working anymore because of resistance are urgently needed. Stewardship programs to avoid non-evidence based use of antibiotics and to promote appropriate dosing are key to preventing further emergence of antibiotic resistance and poor outcomes for patients. Countries must review carefully how they buy and price antibiotics, to reward innovative new drugs without encouraging unnecessary use of new antibiotics.

Vaccines can prevent infections and lower the demand for therapeutic treatments leading to reduced usage of antimicrobials and in turn slowing the rise of drug resistance. The experience with vaccination programs for *Streptococcus pneumoniae* and *Haemophilus influenzae* are prime examples of what can be achieved. By reducing infections and limiting their transmission, vaccines allow drugs to be used

more sparingly and under closer supervision thereby extending their utility. Therefore, vaccines should be used more widely and used together with antibiotics to produce synergistic gains in public health. As such, vaccine development for infectious diseases is a critical part of the solution to AMR and should be eligible for the same incentives being recommended for antibiotic development.

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## **Ethics and compliance in global pharmaceutical industry marketing and promotion: The role of the IFPMA and self-regulation**

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Companies in many industries are engaging in a changing business environment where the community is expecting greater transparency and ethical standards than in the past. This has been for a variety of reasons associated with globalization, technological and social changes. The pharmaceutical industry is one industry where such issues are regularly under the spotlight. In this context the IFPMA works with its member companies and national associations to enhance the agenda of self-regulation and ethical behavior. The global IFPMA Code of Practice, and the many national industry association codes that implement it, have evolved over time to help the industry take the lead in driving greater ethical standards and transparency. This article will review the current international business literature on ethics generally, review the functions and evolution of the IFPMA Code of Practice and examine some of the more recent evidence and analysis of the role of pharmaceutical industry codes, ethics and reputation in the pharmaceutical industry.

Keywords: Ethics, compliance, pharmaceutical, codes, transparency

### **1. Introduction**

In response to a changing business environment, the pharmaceutical industry has made significant efforts toward ensuring compliant and ethical business practices in its marketing and promotion. These efforts have been directed at both to the industry's own operations and its interactions with other stakeholders in the health system, such as healthcare professionals, patients and patient organizations. Changing industry dynamics, new models of business, shifting regulation and legislation, and changing community expectations are all driving significant evolution in the self-regulation model of compliance and ethics of the pharmaceutical industry. This article examines the evolving landscape of industry self-regulation of marketing and promotion through different institutions and organizations, particularly focusing on the role of the International Federation of Pharmaceutical Manufacturers and Association's (IFPMA) in this evolution. The various pharmaceutical industry associations and companies that are members of IFPMA have also contributed to this evolutionary industry self-regulatory model. The efforts of the pharmaceutical industry over the

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last few decades demonstrate the growing importance of self-regulation in marketing and promotion and the industry's emphasis on compliance resulting in sustained relations within the healthcare system. It is an example of industry self-regulation at work.

## **2. Current pressures for change in business ethics**

The pharmaceutical industry is not unique in facing an evolving ethical and regulatory environment. Many industries are facing increased calls for observance to greater ethical standards and be seen to be operating by those standards [1,2]. Businesses are facing greater scrutiny of their operations and business models are changing as community expectations are changing and because of globalization [3,4]. Factors influencing this growing push for a new ethical basis for business include globalization, greater community awareness of the impacts of business on social and environmental issues, the development of international agreements and organizational guidelines on ethics and rights, economic crises, and the growth of transparency generally with developments in technologies such as the internet and social media [5]. As the world is coming together, businesses are under more scrutiny now than ever. Moreover, there is a discussion in the international business literature whether the adoption of new ethical standards and engagement in corporate social responsibility is part of an emerging new view of global governance [6].

In response to these pressures, there have been a variety of international and national initiatives by business, governments and international organizations to develop principles, codes, frameworks, regulations and legislation to establish global ethical standards for business. For example, at the national level countries such as the United States and the United Kingdom have introduced recent legislation to address bribery and corruption that has jurisdiction over companies operating in other countries. At the international level, organizations such as the OECD and the United Nations have undertaken a range of initiatives to introduce global ethical business standards [7]. The OECD's instruments to enhance business ethics and the UN activities for business ethics improvement have both acknowledged current global trends in the pharmaceutical industry, indicating that there can be alignment between the interests of society and those of investors [8]. However, the aforementioned pressures and improvements suggest that regulatory environments and competition within the industry reinforce the importance of strong ethical governance [2].

## **3. Evolution of pharmaceutical industry codes and IFPMA's role**

In the pharmaceutical industry, trust and ethics are particularly important. As a key part of healthcare system, the ethical basis on which the companies in the industry interact with each part of the healthcare system takes on a special level of importance.

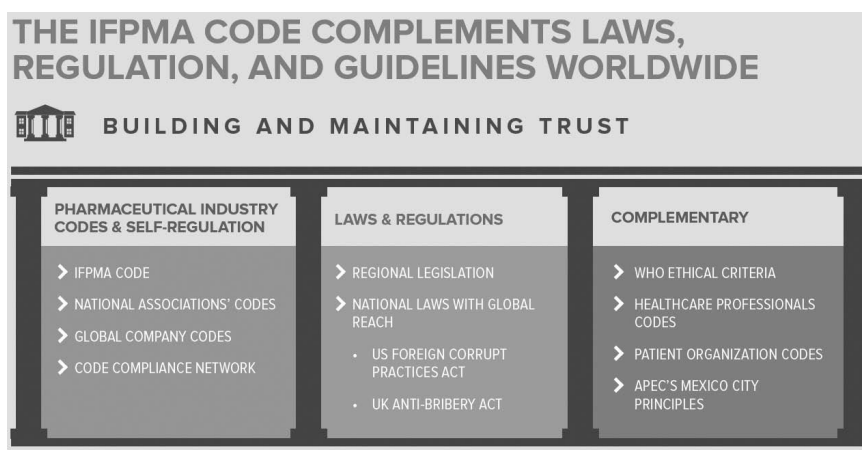


Fig. 1. Interaction between pharmaceutical industry codes and other regulations and guidelines [17].

Of particular importance is the relationship between companies and healthcare professionals and patients, and the way that the industry promotes and communicates to these stakeholders. As consumers become more enlightened and empowered to learn about the industry, many companies have developed their strategies to ensure a transparent relationship between industry and consumer. This has been part of a global effort on the part of the pharmaceutical industry, implemented at the company, national and international level.

The pharmaceutical industry has taken a range of efforts over the years to ensure ethical communication and interaction between healthcare professionals and patients [9]. These efforts have been designed to ensure that the information, where permitted, is balanced, accurate and centered on what is best for the patient. "In these interactions, it is essential that governments, the healthcare community and patients are confident that pharmaceutical companies, wherever they operate in the world, act in an ethical and professional manner [10]."

Since 1981 when it was first introduced, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA)'s Code of Practice has served as a basis for the creation of national codes of conduct for pharmaceutical industries all over the world. Through this Code, together with the various national industry association codes around the world that implement it, the pharmaceutical industry has adopted a self-regulatory model of ethical compliance.

The IFPMA Code of Practice, together with national industry association codes, complements other regulations, laws and guidelines that together regulate the ethical compliance of the pharmaceutical industry. As can be seen in Fig. 1 industry codes of practice coincide with government legislation and regulation, such as the United States' Foreign Corrupt Practices Act and the United Kingdom's Bribery Act, as well as codes of practice for healthcare professionals, patients, and guidelines issued by organizations such as the World Health Organization (Fig. 1).

The IFPMA's Code of Practice is a model of self-regulation for pharmaceutical industry's activities in medicines promotion, communication and interaction with key stakeholders such as healthcare professionals, medical institutions and patient organizations. Although self-regulatory, the IFPMA Code is not voluntary. The Code is a condition of membership to the IFPMA for both member companies and national associations. By virtue of membership, all 30 pharmaceutical companies and 48 national associations of IFPMA are required to observe and implement the IFPMA Code. Often the national association codes contain more detail about what is required at the national level and are responsible for implementation of the more detailed code in their own country. Codes generally have compliance and enforcement mechanisms built into them as part of the system of ethical compliance. In many cases, companies' own compliance provisions go beyond the requirements of the IFPMA and national codes [9].

The most recent edition of the IFPMA Code of Practice covers the following areas of ethical interaction [10]:

- Basis of Interactions
- Pre-Approval Communications and Off-Label Use
- Standards of Promotional Information
- Printed Promotional Material
- Electronic Materials, including audiovisuals
- Interactions with Healthcare Professionals
- Samples
- Clinical Research and Transparency
- Support for Continuing Medical Education
- Interactions with Patient Organizations
- Company Procedures and Responsibilities
- Infringement, Complaints, and Enforcement

The IFPMA Code has been revised and updated on any number of occasions since its inception in 1981, as have the national industry association codes. For example, the 2012 revision of the IFPMA Code of Practice inserted new principles into the Code alongside the provisions in recognition of the fact that one code cannot anticipate all potential issues in all countries. The principles attempt to establish minimum standards for all codes and pharmaceutical industry ethical interaction around the world. The eight principles are:

1. The health-care and well-being of patients are the first priority for pharmaceutical companies
2. Pharmaceutical companies will conform to high standards of quality, safety, and efficacy as determined by regulatory authorities
3. Pharmaceutical companies' interactions with stakeholders must at all times be ethical, appropriate, and professional. Nothing should be offered or provided by a company in a manner or on conditions that would have an inappropriate influence



4. Pharmaceutical companies are responsible for providing accurate, balanced, and scientifically valid data on products
5. Promotion must be ethical, accurate, balanced, and must not be misleading. Information in promotional materials must support proper assessment of the risks and benefits of the product and its appropriate use
6. Pharmaceutical companies will respect the privacy and personal information of patients
7. All clinical trials and scientific research sponsored or supported by companies will be conducted with the intent to develop knowledge that will benefit patients and advance science and medicine. Pharmaceutical companies are committed to the transparency of industry-sponsored clinical trials in patients, and
8. Pharmaceutical companies should adhere to applicable industry codes in both the spirit and the letter. To achieve this, pharmaceutical companies will ensure that all relevant personnel are appropriately trained.

Similarly, revisions to the IFPMA Code of Practice over the last 10 years have led to new developments such as new restrictions on gifts and hospitality, updates to code complaint procedures, transparency, interactions with patient organizations, new provisions on continuing medical education and advisory boards, and requirements for company staff to be trained on code and compliance matters [10].

The current pressures on the pharmaceutical industry to improve ethics have enabled the industry codes to be more representative of sound business practices than laws or regulations. Industry codes can be proactively modified to reflect current needs and trends, and can directly address the criticisms or gaps in practices in a timely and efficient manner, arguably in a more timely and effective manner than other international regulatory efforts could achieve.

In addition to ongoing evolution of the IFPMA Code of Practice, other initiatives at the international level have helped bolster the global pharmaceutical industry's ethical framework. IFPMA has released reports for guidance to companies and national associations on topics such as sponsorship of meetings and events [11], and working with other global healthcare associations to release a Consensus Framework on Ethical Collaboration between Patient Organizations, Healthcare Professionals and the Pharmaceutical Industry [12]. This latter initiative is helping to encourage dialogue at the national level on ethics between various stakeholders groups in a number of countries. IFPMA also conducts capacity building activities in member countries and regions with industry staff and external stakeholders to build local knowledge and awareness of ethical standards, the IFPMA Code of Practice, and the importance of maintaining an ethical framework of business interaction more generally.

This capacity building work has included engagement with regional organizations, particularly the Asia-Pacific Economic Cooperation (APEC) forum. IFPMA has contributed to the establishment of The Mexico City Principles for Voluntary Codes of Business Ethics in the Biopharmaceutical Sector [12] which were agreed by APEC countries in 2011 and based on the IFPMA Code of Practice [13]. The agreement

and subsequent supporting work is designed to establish ethical business practices and codes of practice in pharmaceutical industries in APEC countries.

Of course, pharmaceutical companies themselves are developing more comprehensive internal ethics and compliance structures. The growth in internal compliance processes and teams within companies is another reflection of the growth in industry self-regulation [9,13].

#### **4. Impact**

The efforts by the global industry to develop and evolve its self-regulatory model of compliance are having an impact. The result of international collaboration on ethics and compliance initiatives has led to an international framework of self-regulation for the global pharmaceutical industry's marketing and promotion activities.

For example, many national codes have been updated and expanded over the last 10 to 20 years, both in developed and emerging markets. Code revisions at the national level occur periodically in various countries. One IFPMA survey found that most industry associations had completed a revision of their national code within the last few years of the survey [14]. Each of these expansions has aimed at building the industry's reputation and ensuring that industry codes are relevant to the evolving nature of health systems and community expectations. Whilst necessarily often going into more detail at the national level than the global code, the IFPMA Code of Practice provides a benchmark for these national codes. National associations have introduced variations in things such as reporting systems, pre-approval activities and complaint handling procedures [14].

There is also some evidence that industry self-regulatory activity is leading to improved ethical behavior. Data from a study of UK and Sweden self-regulation conducted from 2004–2012 reported that the number of complaints and cases ruled in breach of the code on a yearly basis decreased by an average of 5 cases per year for both countries [15]. Similar trends have been reported in Australia, where the number of annual code complaints has fallen significantly since the mid-2000s [16]. Whether these trends are primarily due to national codes per se, or a combination of codes together with national and international regulation is difficult to determine from the data. However, clearly the number of cases in this sample of countries has been falling, a reflection perhaps of the improving ethical behavior of the pharmaceutical industry.

Another example of the global industry impact can be seen through the results of the APEC-business ethics program. Since 2011, the Business Ethics for APEC SMEs Initiative enabled more than 1,000 individuals from approximately 650 organizations in the 21 APEC countries to participate in 13 initiative programs [18], establishing it as one of the largest ethics mentor networks in the Asia-Pacific region [19]. In 2015, APEC recorded that 60 biopharmaceutical associations had established new pharmaceutical codes of ethics, representing 14,000 companies in the region.

## 5. Conclusion

Trust and ethics are key to the pharmaceutical industry and the broader healthcare sector. Having comprehensive code compliance and business ethics frameworks for marketing and promotion, and being able to demonstrate these, are important to the pharmaceutical industry's reputation and its ability to provide patients with the care they need. With this in mind national and international institutions will continue to update their codes and expand their reach to the global audience.

The evolving ethical and compliance standards operating at the national and international level in the pharmaceutical industry are an example of the global evolution of international business ethics seen across many industries. The industry has adopted a self-regulatory model that has complemented and supported other initiatives in the regulatory or legislative space, as well as individual pharmaceutical company ethical programs.

The industry's efforts to upgrade and develop its ethical and compliance framework, such as the activities of the IFPMA and its member associations and companies, are an example of the broader trend towards greater business ethical frameworks across all business sectors.

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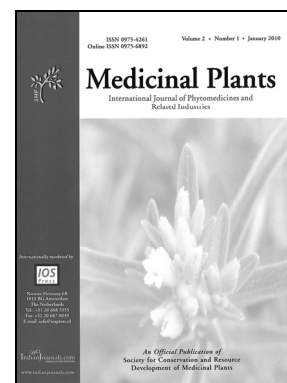
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