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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[1] 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].[2] We define innovation[3] as "a

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[1]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.

[2]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.

[3]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 in to 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].[4] 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.[5] 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

[4]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.

[5]Data from 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 healthcare 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[6] 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

[6]Examples of novel medicines developed in domestic markets are: H1N1 influenza vaccine by Sinovac in China, Meflian 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;[7] 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

[7]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 though 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.[8] In particular, we find the number of clinical trials depends on market access potential (e.g. China and Russia), patient

[8]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 these 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)[9] 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

[9] 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].

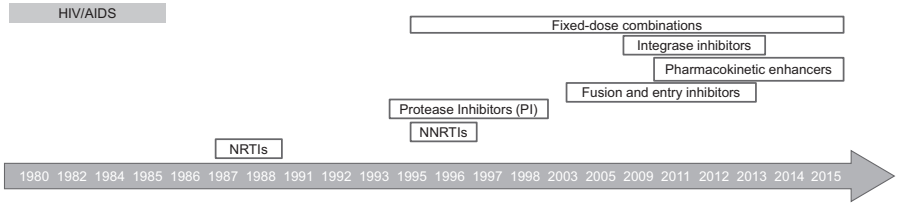

Fig. 1. The evolution of innovation in HIV. Source: CRA analysis.

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)[10] 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

[10]The 2015 WHO recommendations have succeeded the 2014 WHO recommendation that ART should be initiated in all individuals with CD4 count $<$ 500 cells/mm3.

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 multilateral 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[11] 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)[12] 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

[11] 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/.

[12] 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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