REGIONALIZING PHARMACEUTICAL PRODUCTION AND INNOVATION

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Accelerating Vaccine Production for Africa

ACCELERATING VACCINE PRODUCTION FOR AFRICA

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About this Initiative

The initiative on Accelerating Vaccine Production in Africa (AVPA) focuses on identifying the key challenges and opportunities for building domestic capabilities for vaccine manufacturing in the region. It is centred around creating a centres of excellence network in the region that offers cutting edge inter-disciplinary analysis on complex questions related to pharmaceutical production and innovation and helps to build a community of scholars as part of an agenda of strengthening R&D and collaborative learning ecosystems on the topic across several African countries. The initiative combines this with a series of evidence based, policy advisory activities focused on bringing together the private, public and academic sectors in Africa with external counterparts to train talent and increase innovation investments in Africa.

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Regionalizing Pharmaceutical Production and Innovation

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Abstract

In this paper, we address the question of successful establishment of regional production facilities in LMICs from both a design and a management perspective. Given the importance and urgency of current initiatives, we take as a starting point that replicating production facilities in each and every country might be inefficient and costly, and call for resources that currently do not exist, and that a systematic approach to creating a network of supply on the continent would be preferable.

The paper begins with a discussion on regionalizing production from a development and health perspective. It then proceeds to discuss the variety of models available to choose from, highlighting questions of technology, financing and other production incentives. In its final section, it discusses governance issues, and the political and policy decisions that may effectively influence the regionalization of pharmaceutical production.

Keywords

Regional production, innovation, pharmaceutical manufacturing, low- and middle-income countries, value chains, health security, access to medicines, technology transfer.

JEL Classification: I14, I15, I18, L11, L12, L13, L52

* Equal Authorship; names are listed in alphabetical order.

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1. Introduction

One of the main lessons of the COVID-19 pandemic is that low- and middle-income countries (LMICs) face considerable risks and uncertainties when relying on a small number of pharmaceutical producers in a crisis. Reasons other than differential income may lead to vulnerability, including differential bargaining power in international transactions, supply prioritization by private firms, and military/strategic discord. All of these worsen pre-existing social and other inequities in health care, aggravate technology dependence and reinforce low innovation capacity.

Accelerating 'localization' of production of pharmaceutical products[1] in LMICs has been proposed as a potential way to address such supply vulnerability. This is by no means a new subject. Since the 1960s, a number of LMICs have invested in promoting production of pharmaceuticals to reduce external dependence. The result is significant pharmaceutical production in largely (though not exclusively) a number of middle-income countries, but this often involves the formulation of less complex products. In general, the experiences suggest significant difficulties not only in enabling pharmaceutical production, but also in moving up the value chain to reliably produce the active drug substances that form the core of the production activities.

Applying these insights to current discussions, one can start from a 'relatively' self-evident proposition that building production capacity in each LMIC is neither practical nor sufficiently cost-effective. This is definitely so from a capability's perspective, given the difficulties in bringing together the skills and human resources, finances and technologies required to enable such activities from the ground up. One could also argue that from a market perspective, each and every country engaging in building pharmaceutical production capacity would lead to a 'wastage' of investments, and potentially result in too much supply in some categories of pharmaceutical products (that are easy to produce) and not enough in others (which are really needed), thus not necessarily ameliorating the current situation regarding access to medicines.

What would be an ideal combination of resource-sharing for production of pharmaceutical products that could cater to building capacity sustainably, and also promote access to medicines? Industrial production approaches point to clustering of

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***** Equal Authorship; names are listed in alphabetical order.
This paper builds on ongoing work and interviews by authors with a range of companies, international agencies and regional actors engaged in fostering pharmaceutical production.

[1] In this paper the term 'pharmaceutical products' is used broadly to include diagnostics, therapeutics and vaccines, regardless of their composition or mode of manufacture, except as may be specifically distinguished.

production activities as a means to resolve this issue. In the pharmaceutical sector, this has been used successfully in many instances. In a country such as India, with a very large population and geography, an array of policies has been adopted seeking to concentrate production in designated pharmaceutical production zones to take advantage of resource sharing.[2] This is not to say that most production in India is located within such zones, but that they have been used to leverage economies of scale and scope and to promote productivity to a significant extent. The same is true more generally in other instances, such as Brazil, where development policy has explicitly focused on developing a health-based industry complex to leverage similar synergies.[3]

In general, these initiatives build on the fact that pharmaceutical manufacturing is a complex endeavour involving various links in a production chain, and that much more is required to move firms from supply to assembly to manufacturing and innovation in this complex sector, other than sustainably investing in plant and production facilities. If one examines the success of the industries in India and China, it is evident that a major advantage is that in each country a network of suppliers inputting into the various parts of the production chain has evolved, providing the requisite complementarities for manufacturing. This presents major cost advantages, which also feed into expansion of innovative activities. In stark contrast, when expertise, equipment and materials must be imported from abroad, the cost of goods for production remains higher despite localization of production, delays are common, and significant hurdles in scaling up local manufacturing capacity persist.

The requirements for the production and innovation of different types of pharmaceutical products are not the same. As opposed to active pharmaceutical ingredients (APIs), the common base ingredients of drugs until recently, newer biologic products are generally produced in bioreactors, and the inputs include biologic materials of different kinds. Small molecule chemical products are produced in stages, beginning with synthesis from basic elements/chemicals into more complex compounds. Various synthetic chemistry and biological processes are involved in creating new and different combinations, typically carried out in reactors.[4] The resulting complex compounds are then 'formulated' with stabilizing substances into pharmaceutical products suitable for use by humans, involving delivery systems of various kinds, such as capsules, tablets or injectables. Biologic and small molecule chemical drugs are highly dependent on the purity of ingredients and the conditions under which manufacturing is undertaken. Because of the sensitivity of production processes, continuous, reliable supplies of inputs are important, including energy and water (which in any case requires advanced filtration).

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[2] See World Health Organization, 'Indian Policies to Promote Local Production of Pharmaceutical Products and Protect Public Health', Geneva, 2017, https://www.who.int/phi/publications/2081India020517.pdf

[3] See, for example, A.L. d'Ávila Viana et al., 'Development policy for the Brazilian health industry and qualification of national public laboratories', *Cad. Saúde Pública* 2016; 32: S2, http://dx.doi.org/10.1590/0102-311X00188814

[4] See, for example, CordenPharma International, 'Small Molecules', https://www.cordenpharma.com/apis/small-molecule- api-development-manufacturing/

The newest types of pharmaceutical products, such as those produced through messenger ribonucleic acid (mRNA) synthesis, rely in part on genetic sequencing equipment.[5] The vaccine materials initially created by sequencers do not require living cells for reproduction, and this reduces the time needed for producing quantities of vaccines. However, the delivery systems for the current generation of mRNA vaccines involve encapsulation in nanoparticles, which involves a new and complex technology. While aspects of mRNA production may facilitate the establishment and operation of facilities in lower-income environments, other aspects present technological challenges. There is some opinion that establishing mRNA facilities—particularly using modularly manufactured pharmaceutical units that are regulatory compliant—may increase the viability of production in lower-income environments, and efforts are under way to operationalize this.

The possibility of the establishment of 'regional' production capacity in LMICs has been discussed.[6] This raises certain important questions. Perhaps the most important: What should such production capacity focus on (older drug molecules, biologics, monoclonal antibodies, vaccines, and of which kind)? Is the emphasis on regional production sufficient for some technological platforms and not others, to build sufficient back-up capacity for production in a region that is currently 'lagging' behind if the concern of any particular country is to be assured of adequate supplies in the event of a pandemic or other emergency?[7] That is, will it be sufficient if production capacity is established in particular pockets of technologies/products? Relatedly, is it enough if such production capacity is nearby and jointly managed, rather than within the territory of the country itself, to ensure expeditious and adequate supplies of the products?

As a simple illustration, if for e.g., Nigeria is concerned about access to vaccines in a pandemic, would the existence of a vaccine production facility in South Africa be preferable in some way to a similar facility in Germany? We expect the answer to that would be 'it depends'. Equally, is the transfer of fill-and-finish capacity from a producer elsewhere to a local producer enough to ensure sufficient capacity for the future? The answer to this would also depend on a number of factors. As with any 'pooling' effort, the efficacy of any regional arrangement to promote access to medicines will depend on its design and management structure.

Design is critical because building capacity in pharmaceutical sciences is not just a matter of setting up institutions for research and development (R&D) and product development separately but will require fostering connectivity and learning linkages between production (and technology transfer), on the one hand, and building in-

[5] N. Chaudhary, D. Weissman and K.A. Whitehead, 'mRNA vaccines for infectious diseases: principles, delivery and clinical translation', *Nature Reviews Drug Discovery* 2021; 20: 817–838. doi:10.1038/s41573-021-00283-5.

[6] See F. Abbott, R. Abbott, J. Fortunak, P. Gehl Sampath and D. Walwyn, 'Opportunities, Constraints and Critical Supports for Achieving Sustainable Local Pharmaceutical Manufacturing in Africa: With a Focus on the Role of Finance', Final Report, 18 March 2021, Nova Worldwide Consulting, https://nova-worldwide.com/OSF-PHP_report

[7] P. Gehl Sampath and J. Pearman, 'Local Production of Vaccines: A Strategy for Action', *Global Policy Journal* 2021, https://www.globalpolicyjournal.com/articles/health-and-social-policy/local-production-covid-19-vaccines-strategy-action

house capabilities for product and process development, on the other. A number of questions become relevant. What is the strategy in relation to providing the capabilities component?[8] Does the design build on existing strengths for production? What safeguards/plans exist to maximize the linkages between the regional hub and the rest of the innovation capacity in the countries where it is planned?

A number of these questions are also influenced by the management structure. That is, who makes the decisions and how are they carried out? So, as an initial matter, one might suggest that if a facility set up for purposes of regional production were managed by a representative group of countries regardless of where it was set up, allocation issues for production, eventual R&D connections and supply might be better addressed.

In this paper, we address the question of successful establishment of regional production facilities in LMICs from both a design and a management perspective. Given the importance and urgency of current initiatives, we take as a starting point that replicating production facilities in each and every country might be inefficient and costly, and call for resources that currently do not exist, and that a systematic approach to creating a network of supply on the continent would be preferable.

The paper begins with a discussion on regionalizing production from a development and health perspective. It then proceeds to discuss the variety of models available to choose from, highlighting questions of technology, financing, and other production incentives. In its final section, it discusses governance issues, and the political and policy decisions that may effectively influence the regionalization of pharmaceutical production.

2. Regionalizing production for development of the pharmaceutical sector

Historically, regionalization has been suggested as an option for optimizing production and economic growth when countries that are relatively close to one another are also likely to share commonalities along dimensions of culture, language, ethnographic trends and preferences, and that often these similarities can be used to expand the region's overall economic activity. There is a current focus on regionalization for a number of reasons. A primary one is the search to maintain sovereignty by pooling resources in areas of economic management where otherwise countries are too small to act alone.[9]

Ongoing work on inter-firm networks lends support to how regional development can be fostered through 'strategic coupling' of firms and regional economies, to drive

[8] P. Gehl Sampath, 'Building Capabilities for Local Production of Vaccines: The mRNA Hub in South Africa', International Labour Organization, Geneva, November 2021.
[9] M. Schiff and L.A. Winters, 'Regional Integration and Development', World Bank and Oxford University Press, Washington, DC, 2003, p. 6, https://openknowledge.worldbank.org/handle/10986/15172

certain kinds of development processes that would otherwise not occur.[10] In these studies, a number of factors are identified as critical enablers of value creation and regional economic development. Agglomeration of scale— something that is critical in a number of industries, including in pharmaceutical production—occurs when firms interact at the regional level, through specific institutional incentives to engage in the industrial upgrading of their production systems.[11]

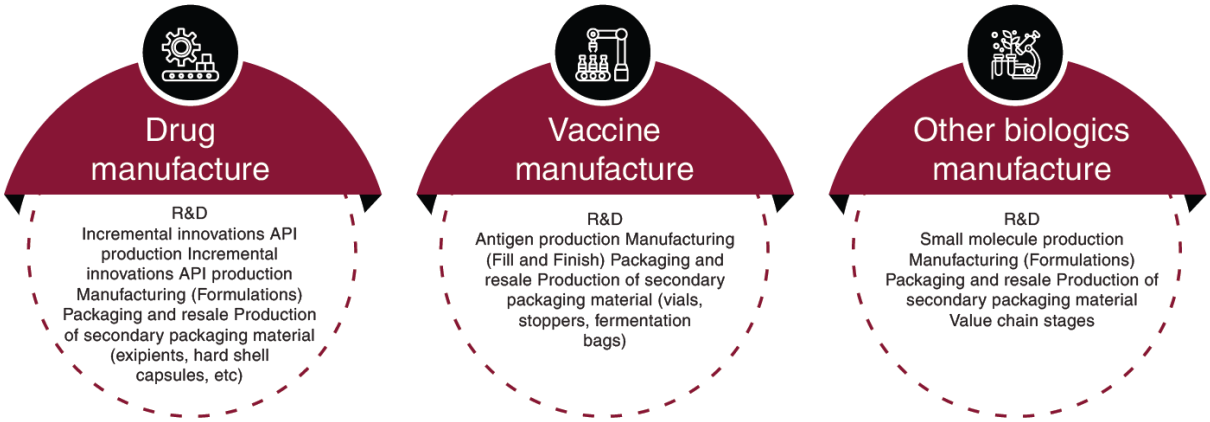
2.1. Agglomeration of scale: Rationale for interventions

The process of agglomeration of scale in regionalization can be achieved in two different ways. One, it can arise automatically when firms connect in an autonomous manner. In these instances, it is the organizational structures of a global/regional company's production system that explores how specific regional economies can be slotted into specific production networks or value chains.[12] But this kind of networking into existing production chains does not always occur on its own.

Many companies and sectors in the global South have historically faced difficulties in forging this kind of strategic coupling within value chains and networks, and leveraging learning effects from it.[13] Particularly, although it may be clear to local firms that development and upgrading requires establishing such connections, they remain hard to break into. Often, even after connecting into production networks, local companies can get locked into specific production relationships that do not contribute to learning, and expansion within the value chain.[14]

[10] N.M. Coe et al., ''Globalizing' regional development: a global production networks perspective', *Transactions of the Institute of British Geographers* 2004; 29(4): 468–484.
[11] See A. Amin, 'Spatialities of Globalisation', *Environment and Planning* 2020; 34: 385–399.
[12] G. Gereffi and R. Kaplinsky (eds), 'The value of value chains: spreading the gains from globalization', *IDS Bulletin* 2001; 32.
[13] R. Horner, 'Strategic decoupling, recoupling and production networks: India's pharmaceutical industry', *Journal of Economic Geography* 2013; 14: 1117–1140.
[14] Ibid. Also see R. Lema, R. Raboletti and P. Gehl Sampath, 'Innovation Systems in Developing Countries: Co-evolution of Global Value Chains and Innovation Systems', *European Journal of Development Research* 2018; 30: 345–363.

Figure 1. Pharmaceutical production in a global value chain/production network perspective



Source: P. Gehl Sampath, 'Building Capabilities for Local Production of Vaccines: The mRNA Hub in South Africa', International Labour Organization, Geneva, November 2021.

In the pharmaceutical sector, the transition from one stage to another in the production process is not easy. Local firms in LMICs that venture into production find it increasingly difficult to move from formulating drugs to producing the active drug substance in the case of simple drugs. The same is true in the case of vaccines, where establishing fill and finish capacity is relatively more difficult than formulating drugs, and the shift from fill and finish to more complex stages of production (through backward integration) calls for a variety of competencies in production and regulatory compliance that are often not available.

In this sector, although it has been tempting to exploit the relative merits of production networks/value chains, not much evidence exists to support the idea that the 'modularization of production' into several stages has created specific entry points for companies from different regions.[15] Existing studies find that in economies where both global and national companies co-exist, moving up the value chain in production requires significant effort by local companies.[16] This may be because pharmaceutical production remains more knowledge-intensive than several other

[15] See G. Hollinshead, 'The tortuous ascent of global value chains – the case of pharmaceutical R&D in China', *Critical Perspectives on International Business* 2017; 13(3): 244–262.
[16] See, for example, the value chain analysis of Jordan's pharmaceutical sector, which showcases many of these difficulties: Deutsche Gesellschaft für Internationale Zusammenarbeit GmbH, 'Value Chain Analysis for the Pharmaceutical Sector in Jordan', Bonn and Eschborn, Germany, 2019, https://www.giz.de/de/downloads/Value%20Chain%20Analysis%20of%20the%20Pharmaceutical%20Sector%20in %20Jordan.pdf

sectors where production networks have promoted integration of new firms.[17] As a result, both the strategic requirements of skills and talents are not often met in LMICs, and the prevalence of patents and intellectual property rights on products and processes acts as an additional barrier to entry in what is already a difficult sector for newcomer firms.[18]

For this reason alone, a number of recent studies suggest that some form of strategic decoupling from global networks to promote regionalization—through purposive policy interventions—could address many of these issues. This second approach advocates the explicit fostering of regional alliances with a focus on enhancing the focus on the dynamics that shape knowledge, capital and labour flows. Here, the pooling of regional assets is a precondition to promote economies of scale in production by facilitating the concentration of knowledge, skills and expertise.

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can potentially translate into economies of scope if there are institutional connections that enable these regions to harness the intangible benefits of learning that are usually the outcome of such an agglomeration.[19] Successful cases where such interventions for strategic decoupling have succeeded (albeit only at the national level) are the Indian pharmaceutical sector[20] and Bangladesh's pharmaceutical sector, where more recent experience with strategic decoupling from global forces to build the production capacity of domestic firms has borne dividends.[21]

[17] Early evidence on the sector confirmed, for example, the assumption that when a large number of low-income countries integrated into the paharmaceutical value chain, they continued to produce low-technology-intensive activities in an otherwise high-technology-intensive sector. As a result, their presence in the sector, *prima facie*, did not lend evidence to their being active in high-technology-intensive activites. See, for example, UNCTAD, 'Toward a New Developmental Architecture for Least Developed Countries', LDC Report, Geneva and New York, 2010.
[18] A World Intellectual Property Organization (WIPO) report from 2017 notes "[t]he intangibles share is especially high – and more than double the tangibles share – for pharmaceutical, chemical and petroleum products" in global value chains. See WIPO, 'World Intellectual Property Report 2017: Intangible Capital in Global Value Chains', Geneva, 2017, p. 11, https://www.wipo.int/edocs/pubdocs/en/wipo_pub_944_2017.pdf
[19] N.M. Coe et al., *supra* note 10, p. 470.
[20] R. Horner, *supra* note 13.
[21] P. Gehl Sampath, 'Pharmaceutical Manufacturing in Bangladesh: A Success Story, but What Can We Learn?', Federation of East African Manufacturers Association, FEAPM Advocacy Series, Print 1, 2020. See also A. Amin, *supra* note 11.

2.2. The benefits of successful regional agglomeration

For countries that cannot strategically decouple to promote and boost production on the backbone of their internal strengths alone, regionalization can help pool assets for critical inputs in the pharmaceutical sector, namely:

- pooling scarce human resources and skills.
- creating regional industrial clusters of production (and, by extension, learning and collaboration).
- pooling R&D investments.
- enhancing the capacity of small business innovation and supporting industrial upgrading.
- creating regional common industry infrastructure for APIs, antigens, fill and finish, and other testing and regulatory compliance requirements; and
- promoting supply networks.

Regional agglomeration can also offer the much-needed push for companies to engage in process and product innovation, which are not isolated phenomena but well interlinked in conventional pharmaceutical production. Particularly, in the pharmaceutical sector, adaptive and incremental innovation activities are non-trivial activities. Reverse engineering, for instance, presupposes a deep understanding of the processes and products, for which design and local value-added remain the initiating point of innovation.

Expanded clustering and regionalization, with a focus on universities and centres of excellence, can potentially mimic the experiences in several other developed countries which have very good sectoral systems in pharmaceutical biotechnology, where interactions between industry, universities and public research institutes and the movement of human capital between these institutions have been critical in building and strengthening the innovation system over time. In these countries, it has been observed that interactions usually involve a range of contract research—collaborative research arrangements with the industry in the research and patenting stages.[22] Such an emphasis can help promote strengths in biologics production and vaccines.

[22] V. Chiesa and G. Toletti, 'Network of Collaboration for Innovation: The Case of Biotechnology', *Technology Analysis & Strategic Management* 2004; 16(1): 73–96.

Clearly, factors that lead to success in such efforts are necessarily different depending on the regions in question, but in general they comprise the issues, actors and local and non-local interventions listed in Table 1.

Table 1. Successful regional agglomeration: Actors, pressure points, configurations, and impacts

Issues	Possible local actors	Non-local actors/ pressure points	Configurations	Impacts
Technology transfer for production and innovation	Local companies public research institutes Skilled and semi-skilled workers	Global companies and their subsidiaries Export standards External experts Export to national/ regional/international markets	Product development partnerships Industrial clusters Joint ventures University–industry collaborations Global production networks Value chains	Training, retraining and employment creation. Tacit know-how transfer Infrastructure and assets
Technology transfer, R&D, and innovation	Local companies public research institutes Centres of excellence R&D hubs	Global companies and their subsidiaries Export standards External experts Export to national/ regional/international markets	Product development partnerships Intra-firm collaborations Joint ventures Technology licensing Strategic alliances Inter-institutional alliances University–industry collaborations	Investment Growth coalitions Technological upgrading Incremental and radical innovations

3. Models for regional production: A discussion

A number of different regional production models exist in which these synergies between local and non-local actors can be fostered. The most important ones include a portfolio strategy (where companies acquire operations abroad but report to a home base), the hub strategy (building regional bases that supply a variety of shared resources), distributed supply chains, South–South collaboration models and the mandate strategy (where specific regions have particular mandates within a carefully calibrated innovation plan).[23] In the pharmaceutical sector, a number of these can be used to promote production in the current context, either alone or in conjunction with one another.

As a preliminary observation, whichever model or combination of models might be employed to promote the build-up of regional capacity, there will be competitive crosscurrents between parties that perceive economic and/or political gains or losses from different approaches. For example, privately owned enterprises tend to value decision-making autonomy and might well push back against governmental participation and/or intervention that affects that autonomy. This pushback can take various forms. A fundamental question is whether and how arrangements can be created that allow for cooperation based on perceived benefits for a substantial enough group of parties to enable the organizational effort. It may similarly be harder to promote the focus on innovation (as opposed to simply production through the establishment of fill and finish facilities as is currently envisaged in several countries), with an emphasis on the participation of public R&D institutions. These routes, nevertheless, will be important to pursue despite the frictions they present, and this section provides several possible models of engaging in such regionalization.

3.1. Model 1: Portfolio strategy: Private-sector decisions

Market forces allocate resources for private companies. In keeping with that, one approach would be to rely on the private sector and market forces to make decisions regarding what and where to produce. Throughout most of the world, private-sector pharmaceutical companies—whether originator or generic—have historically made the decisions about what and where to produce and how to expand their production activities. Even as the global response to the COVID-19 pandemic continues to unfold, a great part of the activity taking part in the pharmaceutical, including vaccine, sector is being driven by private-sector decisions.[24] In particular,

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[23] For a discussion on how these are used in different sectors, see P. Ghemawat, 'Regional strategies for global leadership', *Harvard Business Review* 2005; 12, https://hbr.org/2005/12/regional-strategies-for-global-leadership

[24] Vaccine supply in high-income countries has been dominated by Pfizer/BioNTech, Moderna, Johnson and Johnson, and AstraZeneca. Although in each case the private-sector companies have relied on subsidization and/or government offtake of product, decisions regarding production and distribution have largely been left in the hands of the companies. China has relied on domestically developed and produced vaccines, principally from Sinopharm. Sinopharm is state-owned. India has relied on domestically produced vaccines from private-sector companies (e.g. Serum Institute and Bharat), with Serum Institute producing under licence from AstraZeneca/Oxford for India and elsewhere. The Russian Federation has relied on domestic

AstraZeneca has embarked on a number of licensing arrangements with companies in LMICs, notably SK Bioscience (South Korea), Fiocruz (Brazil), R-Pharm (Russia) and the Serum Institute of India (India) for the production of COVID-19 vaccine Vaxzevria and CoviShield (brand name); the Chinese company Sinopharm has licensed Bio Farma (Indonesia), Instituto Butanan (Brazil) and Pharmniaga (Malaysia) for the production of its vaccine CoronaVac; and Johnson and Johnson has licensed both Aspen Pharmaceuticals (South Africa) and Biologicals E (India) for the production of the Janssen COVID-19 vaccine.[25]

More generally, insofar as specific LMIC markets represent a significant investment opportunity for private-sector pharmaceutical companies, investments in supply expansion to cater to and capture those markets will continue. To facilitate these processes, governments could elect to pursue policies that would attempt to make pharmaceutical investment attractive for global companies, and it is fair to assume that profit-motivated pharmaceutical companies would address the market in an economically rational way. For example, if Company A chooses to spend $200 million building a manufacturing plant for a particular drug in Country X, it is doubtful that Company B would decide to build a manufacturing plant for the same drug in Country X, because the market would be over-supplied and prices would drop.[26] The private companies would essentially allocate the market among themselves based on their own demand and profitability assessments, the willingness to pay, and competition.

A. Establishing baseline conditions

As each private company makes its decision on where to invest, it will seek the best possible investment terms from the host country, and this may not necessarily coincide with the goal of building capacity or facilitating the creation of a domestic pharmaceutical sector. In a regional market that is left open to bargaining between each government and each company, there will be an incentive for the governments to offer terms more favourable than their neighbours to locate the companies within their boundaries to extract employment and other synergies in the longer run. This will put significant leverage in the hands of the private-sector companies, which will scout locations based on specific advantages, and the governments may be less likely to secure benefits such as commitments to transfer of technology, tacit know-how spill over and local investment in a wider range of products that they might otherwise obtain. The model of investment would be largely private, and, to a large extent, competition for investment from large companies will produce a system that will, for the most part, benefit investors more than the countries themselves.

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development and production of Sputnik V. The Sinopharm and Sputnik V vaccines are also produced and distributed through licensing and joint ventures in Latin America, India and elsewhere.

[25] For more such commercial licensing arrangements, see Table 1, P. Gehl Sampath, 'COVID-19 and the Need for a New Global Health Diplomacy', *Harvard Public Health Review* 2021; 29, https://hphr.org/29-article-gehlsampath

[26] This illustration is naturally simplified in the sense that the amount to be spent and potential market demand will depend on the company's perceptions of profitability and sales.

In this regard, one option would be for governments in a region to reach a common understanding regarding the maximum of incentives they will offer to foreign investors, to ensure some alignment between these investments and other domestic and regional objectives. These incentives could include a regional buy-back of products from companies in exchange for specific conditions of production, technology exchange and investment, including the creation of joint ventures in specific instances between global and local companies.

Consider, for example, that the Organisation for Economic Co-operation and Development has recently mediated a commitment among high-income countries to charge a minimum corporate tax rate of 15 percent so as to avoid the tendency of governments to use tax reductions to incentivize investment.[27] There are also cases where, based on private-sector decisions on which companies/countries to partner with, local companies are selected for production purposes. In these instances, it is equally important for governments to facilitate the baseline for intervention, to avoid the prioritization of some companies over others in the domestic production and innovation ecosystem.

It will, of course, be tempting for governments to 'out-bid' each other to gain advantage over one another, or to prioritize some firms over others domestically in this process. This can have adverse impacts on the emergence of the sector; to avoid this, monitoring and enforcement of compliance might become necessary with some coordination.

B. Risk of failure

The Andean Pact foreign investment code (Decision 24) adopted in the 1970s represented a strong form of measures attempting to establish uniform 'rebalanced' conditions for direct investment among a regional group in an effort to promote technology transfer through investments.[28] The countries of the Andean area in Latin America sought to establish a consolidated bargaining entity for negotiation with more economically developed countries, and ultimately did not succeed. But the internal political situation within the region was not sufficiently aligned to create a common external bargaining position, and soon weakened.

A number of reasons have been suggested for this, including that there did not exist sufficient political consensus within the various countries from the outset.[29] Whatever the reason, the Andean countries did not enforce their own conditions. The Andean experience suggests the importance of building a shared political understanding and

[27] Organisation for Economic Co-operation and Development, 'International community strikes a ground-breaking tax deal for the digital age', Press Release, Paris, 8 October 2021, https://www.oecd.org/tax/international-community- strikes-a-ground-breaking-tax-deal-for-the-digital-age.htm

[28] See F.M. Abbott, 'Bargaining Power and Strategy in the Foreign Investment Process: A Current Andean Code Analysis', *Syracuse Journal of International Law & Commerce* 1975; 3: 319, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=1977558

[29] See, for example, R. Vargas-Hidalgo, 'An Evaluation of the Andean Pact', *University Of Miami Inter-American Law Review* 1978; 10: 401, http://repository.law.miami.edu/umialr/vol10/iss2/7; and T.A. O'Keefe, 'How the Andean Pact Transformed Itself into a Friend of Foreign Enterprise', *International Lawyer* 1996; 30: 811, https://www.jstor.org/stable/40707283.

a monitored/enforceable set of rules among countries participating in a regionalized pharmaceutical production effort.

3.2. Model 2: The hub strategy: Building regional production bases

From the perspective of coordinated intervention to rectify market failures, perhaps the 'ideal' model for supplying pharmaceutical products throughout a region is to concentrate production in a single geographic location, or in a few earmarked geographic locations in any given region. One reason for such a preference is to allow the establishment of an infrastructure base to support the industry development with a sharing of common costs and pooling of essential and scarce resources for production. Another reason would be that concentration in a single location would facilitate the development of a surrounding network of suppliers, create backward and forward linkages in the region, and facilitate infrastructure investments, all of which can promote the performance of the pharmaceutical firms. Ideally such a regional hub should also include technology-related institutions for research, consultation, skills-building, and training.

A. Geographic selection criteria

Given the potential scale of the costs involved, a principal criterion in the selection of a geographic location for a regional hub should be taking advantage of existing infrastructure and other pharmaceutical manufacturing-related facilities. The challenge in executing a successful hub strategy lies in establishing the right balance between centralization based on current strengths, with some autonomy and connections with the rest of the region.

At a basic level, matters such as the local availability of construction service providers with related equipment is important. And given that a regional hub would necessarily envisage supplying to a wider geography, as well as importing materials and equipment, relatively important factors that reduce the cost of goods would be: the availability of competitively priced infrastructure (water, electricity), easy transport, and information and communication technology facilities. Although human resources are 'mobile' in principle, the availability of work permits and affordable housing, and the relative accessibility of the hub from other parts in the region and outside are also significant factors in attracting the right kinds of expertise. Ensuring that working at a regional hub is attractive for employees is important to maintain continuity and avoid continuous training or retraining of personnel.

B. Pooling considerations

Clustering is a key aspect of localization in the hub model, taking advantage of or creating possibilities for sharing resources among enterprises/other actors located in the hub. In some cases, such as for the synthesis of APIs, it may be productive to envisage common industry infrastructure—such as an API park—and ensure proximity to existing petrochemical complexes where some of the basic components may be sourced. As API production is known to be problematic from an environmental standpoint, location proximate to existing hazardous waste disposal facilities would also be useful.

The advantages and disadvantages of geographic locations are likely to be different when different types of pharmaceutical products are considered, and this paper does not attempt to address all of those variables. Facilities for formulating finished pharmaceutical products are not as resource-intensive as those needed to set up API production. In comparison, again, facilities for manufacturing biologic products rely on much different types of starter materials than small molecule chemical products, and the manufacturing processes are substantially different. There are likely to be different types of advantages by location within a common geographic territory, including access to expert service suppliers, including equipment upkeep and repair, and for materials such as testing supplies, as well as proximity to computer software expertise. Facilities for establishing vaccine production, once again, will depend on a number of prerequisites, including the capacity of the national drug regulatory authority to inspect and conduct lot releases.

The World Health Organization (WHO) mRNA Hub initiative leverages several of these advantages by location. The central actor in the hub is Afrigen Private Limited, a biotechnology company based in Cape Town, South Africa, with technology development, technology transfer and capacity-building responsibilities. The Biovac Institute is the primary spoke in the model, also located in Cape Town. The mRNA Hub is supported by several research centres located in South African universities, and is coordinated through the Department of Science and Technology, South Africa. The WHO has identified additional spokes in Egypt, Senegal, Nigeria, Kenya and Ghana. These countries will be technology recipients, receiving know-how and training from Afrigen Private Limited on several aspects of the use of mRNA platforms for vaccine production.

While this offers some new ways to construct regional production, there remain some unanswered issues. For example, whether the materials used in the production processes for biologics can be shared within a particular geographic territory among different producers deserves additional study. Similarly, whether such hubs can function efficiently when the supply chain elements are not integrated into the production activity also requires some attention. More generally, to the extent governments in the region are considering the establishment of more than one regional hub, that a differentiating factor among the hubs may entail the type of products produced, and the technology platforms that could be employed (see the final subsection on the mandate strategy).

3.3. Model 3: Distributed supply chain

Another potential model would involve a strategically planned distribution of production facilities and related suppliers throughout the region, allocating to different countries the right and obligation to produce certain products for distribution throughout the region.

A. Selection criteria

A distributed supply chain model would provide space for allocating production across a regional geographic territory, thereby avoiding some of the deeper allocation issues inherent in a regional hub model. In other words, the regional hub model envisages a concentration of production in one or several discrete geographic locations, which will serve as the technology development foci. The selected regional hub location would be perceived to advantage the location selected, potentially setting up a competition among countries of the region. For example, in the current constellation of the mRNA Hub in Africa, the newer countries such as Nigeria, Kenya, Egypt and Senegal are configured as spokes, implying that they will act as fill and finish facilities, as opposed to those in technology development activities. So although other countries could participate in the regional hub, there is a clear delineation of roles and responsibilities, depending on how the countries integrate into the regional hub. In stark contrast, the distributed supply chain model offers the possibility of building diversified strengths in different locations within any given region. While there would also be a competitive aspect to a distributed supply chain model, distribution of the production chain would reduce the in-built allocation obstacles.

There are at least two potential approaches to allocation across a region. The first would involve allocating to a specific country (and its enterprises) responsibility for production of a particular product or products, leaving it to that country to determine how to best address supply of the particular product(s). The second would involve allocation of different steps in the production process among countries in the region. For example, as a simplified illustration with respect to small molecule drugs, some countries would be responsible for synthesis of APIs, some for formulation, and some for packaging and labelling. For biologics, as a simplified illustration, some countries could be responsible for producing the active biological materials, others the fill and finish (including packaging), and others could engage in other specialized materials needed for production. Neither of the above approaches need be mutually exclusive. Depending on the state of existing productive capacity, a mix of product responsibility and step responsibility could be envisaged.

Building the distributed supply chain model would entail a detailed survey of existing production capacity for components and finished products within a region and analysing those components for their quality and sustainability of production. The region as a whole might then select the ‘best’ existing candidates for allocation of responsibility to supply the region. To the extent that the governments are proposing to provide financial support for sustainable regional production, those candidates selected would then be the beneficiaries of that regionwide support.

One of the potential advantages of the distributed supply chain model would be that it might allow greater opportunity for participation by the lesser developed countries within the region, either through participation by supply of lower-technology-intensive products or by engaging in less technologically advanced parts of the supply chain (e.g. packaging and labelling). Distributed supply chain models can go hand in hand with regional hubs, and may even be advisable, given that they will help companies

to better cope with the supply crunch for intermediate inputs in pharmaceutical production.

B. Risk of weak links

There is some risk attendant to the concept of the distributed regional supply chain, particularly given that not much evidence supports the ability of countries that are starting out with production to build capacity across all the stages, or to coordinate these efforts (through a policy coordination exercise that remains equally challenging in LMICs). Both the product allocation model and the step allocation model may create a vulnerability should the enterprise within the selected country fail to deliver on the final product range, or should public investments not materialize as anticipated. There are a number of potential reasons for failure, human-made or even driven by natural events. That said, there are ways to address these risks. The first would be to build redundancy into the system. The problem with that approach is that it may also result in inefficient resource allocation. The second would be to identify potential back-up suppliers from within (by choosing more than one country for each step) and outside the region. This could form part of the cross-regional (including South–South) cooperation discussion addressed in the next subsection.

C. Forward and backward linkages

Setting up a distributed supply chain requires some thinking among policymakers on forward and backward linkages that are needed to reduce the costs of production for the products that are prioritized for pharmaceutical production in the region, and ways to enhance coordination among regionals suppliers. These could be different depending on the products—i.e. vaccines versus drugs versus others—and do not necessarily preclude building strong networks with international suppliers and international markets for final sales of products after regional demand has been met. There may also be the need to consider and improve regional transport and trade relations.

3.4. Model 4: South–South collaboration or inter-regional cooperation

It is now over a decade since developing countries surpassed developed countries as major partners of other developing countries for trade in capital goods.[30] The growing economic and commercial interests of many emerging economies have been fuelling market expansion and some level of technological collaboration with other developing countries. To what extent there might be advantages to promoting collaboration or cooperation along developmental lines, such as to promote collaboration among LMICs (including ‘emerging economies’) as compared with promoting collaboration or cooperation with higher-income countries or regions, is a relevant issue from a political standpoint. Dating back to the late 1960s there was a perceived political advantage to ‘South–South’ collaboration in the context of

[30] UNCTAD, ‘South-South Collaboration for Technology and Innovation’, Technology and Innovation Report, Geneva, 2012.

attempting to rebalance disparities in economic development between North and South.

A. Political constellation

Developing-country vaccine manufacturers—now a large alliance of local producers from a range of countries in the global South—might offer an equally important venue for establishing collaborations. Current estimates show that 7 of the top 10 companies based on volumes worldwide in the vaccines market are from the developing-country vaccine manufacturers network[31]. The recent experiences of the firms in this network make them extremely important partners in any effort to build capacity in the developing world. At the same time, there may be points of departure. The question from the standpoint of a region pursuing substantial pharmaceutical self-sufficiency is defining the terms of engagement with another region or group of countries, or even group of firms. That is, using the combined economic and political weight of a region to leverage improved terms of engagement, and doing so while maintaining a competitive market for supply of pharmaceutical products will become an important issue.

There are enormous economic opportunities for investment and trade from a South–South perspective, and the pharmaceutical sector may well offer the entry point for larger emerging economies to engage with other LMICs. The biomanufacturing training hub in the Republic of Korea, recently announced by the WHO, is one such initiative. This training hub, expected to complement the training provided by the mRNA Hub in South Africa, is poised to assist LMICs with technical and other training on operational and good manufacturing practice requirements for vaccine production in LMICs[32].

Within this overall picture, there may yet be a broader, important role for South–South cooperation in areas such as technical education, training and R&D promotion in specific areas of pharmaceutical production that move from singular examples of firm-level cooperation to systematically exploring and promoting relationships.

B. Supply chain integration

Even within a South–South constellation, it should be expected that at the industry level there are often gaps in a production system established by a region anywhere in the world, and the issue of where to fill those gaps will arise. It may be possible to better plan integrated supply chains so as to provide medium-term secure solutions to a comprehensive regional plan. So, for example, certain medium-term supply contracts for specific APIs may be put in place as the region builds up its own API capacity. This may help to solve issues of production in the immediate term, but extended supply chains are more vulnerable to external shocks from a variety of potential causes, including changes in political climate.

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[31] P. Gehl Sampath and J. Pearman, supra note 7.

[32] J.L. Ravelo, 'WHO announces new biomanufacturing training hub in South Korea', Devex, 23 February 2022, https://www.devex.com/news/who-announces-new-biomanufacturing-training-hub-in-south-korea-102740.

3.5. Model 5: The mandate strategy

Industrial economists have long stressed that the emergence of a strong contender in a region and enabling production can promote both intrasectoral (within the sector) and intersectoral (between sectors) spillovers. Over time, this could also be the starting point for the development of regional capacity. This is particularly documented in the economic literature on the East Asian experience, and to some extent on India's and China's impact on pharmaceutical production in the region, as the Flying Geese hypothesis.[33] This, in essence, builds on the principle of dynamic comparative advantage within a region, wherein a first-tier country with more advanced capacity triggers demand for products and processes throughout the region, and promotes the transformation of production structures. In many ways, this would be similar to what is popularly known as the mandate strategy in business economics.

A. Selection criteria

To build this kind of dynamic comparative advantage, a more coordinated vision is required, where certain regions are afforded broad mandates to supply particular products or perform particular roles. A good example of this could be the African Union's vision of producing at least 60 percent of the region's vaccine requirement in Africa by 2040 by way of building three to five regional production hubs that focus on different kinds of technology platforms.[34]

B. Coordination issues

Of all the models discussed here, this is perhaps the most demanding constellation for regional production, requiring significant coordination tasks to offset the risks associated with planning broad production mandates focused on particular locations. A first of these is the choice of products and technology platforms. That is, is there enough complementarity to build capacity broadly for the entire region? Next is the question of how broad production mandates can be made to address variations in local, national or regional conditions for production. That is, can a regional aspiration/target sufficiently advance questions of really building or leveraging regional innovation systems, and if not, what kinds of institutions may need to be created for coordination and implementation of these targets in the region? This would be essential, given that there will be different forms of specialization required to produce different products, using different kinds of technologies, which to a certain extent creates inflexibility.

[33] See K. Akamatsu, 'A historical pattern of economic growth in developing countries', Journal of Developing Economies 1962; 1(1): 325–362.
[34] See African Union and Africa CDC, 'Discussion Paper in Preparation for the African Vaccines Summit', 12–13 April 2021.

C. Risk of failure

Building dynamic comparative advantage within a region will rely on close trade links between countries that can facilitate the creation of production, consumer and learning linkages more broadly.

4. From modelling to practice: Governance issues

Conceptualization of regional strategies for localization of pharmaceutical R&D and production is a necessary predicate to action. A number of governance issues will become critical in establishing regional hubs of the kinds discussed above.

The Association of Southeast Asian Nations (ASEAN) region has made considerable progress in developing a framework for cooperation and coordination directed at assuring vaccine security and self-reliance, including by conducting a baseline study of the existing situation in the region, and the development of the 'Regional Strategic and Action Plan for ASEAN Vaccine Security and Self-Reliance (AVSSR) 2021-2025'. This plan seeks to establish greater regional R&D capacity, as well as to bolster financing for regional production, and coordination of regional procurement. At present, this framework is not the subject of a formal ASEAN institutional arrangement, but rather involves cooperation among the Ministries of Health.[35] The African Continental Free Trade Area (AfCFTA) is another recent initiative seeking to develop and put in place a framework for cooperation that will have a significant impact on pharmaceutical production and regional regulatory harmonization in the region. Among other issues, the AfCTFA is expected to also tackle the question of intellectual property rights on public health[36]

A. Regional procurement

The successful establishment of a regional production hub would be dependent on the existence of sufficient demand for the products from that hub. Experience from countries building the pharmaceutical sector suggests that despite the best of efforts, in the initial start-up phases, the pharmaceutical products from the hub might not be the lowest-priced products. Sourcing in inputs for production in general is associated with higher costs of production when compared to identical products from China and India, where they might be sourced and produced within the same company.

Taking the cost of goods into consideration, a primary issue would be to ensure that regional procurement mechanisms still offer some preferential space for sourcing from regional hubs. Over time, one would anticipate that the hub would become price competitive, but this may still require sufficient policy incentives and support in terms of infrastructure, and tariffs, among others.

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[35] ASEAN, 'Regional Strategic and Action Plan for ASEAN Vaccine Security and Self-Reliance (AVSSR) 2021-2025', adopted 14 May 2021, https://asean.org/wp-content/uploads/2021/10/AHMM-ADOPTED_AVSSR-Strategic-and- Action-Plans-2021-2025-cleaned-version_FINAL.pdf A useful study of the vaccine landscape and the potential for coordination of regional production and procurement in the ASEAN region is Asia-Pacific Hub of the Reform for Resilience Commission, 'Resilience in the Asia Pacific: Vaccines and the "Triple Challenge"', October 2021.

[36] Interview with the AfCFTA Regional Secretariat, Accra, Ghana, 21 March 2022.

Whether and to what extent regional procurement mechanisms can be created and used to promote competitive supply of drugs and vaccines has now become an important question. Broadly speaking, pooled procurement can have several advantages, including transparency in procurement of vaccines and drugs, streamlined processes, financial forecasting and reduced prices (through collective bargaining), quality control and quality assurance, and flexibility to reflect specific country/regional needs.

Two initiatives offer two different models for consideration, having had varying degrees of success in pooling procurement. The first is the Pan American Health Organization (PAHO) Expanded Program on Immunization (EPI) Revolving Fund, which is the central procurer for vaccines and immunization supplies and works by purchasing supplies on behalf of countries in the Latin American and Caribbean region. In this model, the countries participating delegate full authority to PAHO to negotiate, contract and pay suppliers. Since its establishment in 1979, the PAHO Revolving Fund has successfully promoted vaccine supply and immunization for its member countries, expanding from 19 countries in 1979 to 39 countries covering almost all of the Latin American region by 2003.[37] Over time, the Fund has achieved cost savings, promoted the achievement of immunization goals in the region, and helped to constantly expand the portfolio of vaccines available in the region. However, it has faced challenges in some instances—particularly when there are only one or two suppliers—to achieve cheaper prices, or similar prices that have been procured by UNICEF/Gavi by aggregating most of the Gavi 73 (now Gavi 56) markets.[38] A recent study shows that the prices procured by the PAHO Revolving Fund are higher than the Gavi/UNICEF prices for unit doses of the same vaccines, but much lower than those by self-procuring middle-income countries.[39]

The Gulf Cooperation Council (GCC) Group Purchasing Program in the Persian Gulf is a different model. Broader in scope, it deals with medical supplies but makes countries responsible for contracting with and paying producers on their own, after the winning bids have been selected at the regional level. The GCC Program also supports some of the findings on pooled procurement, that when done properly, it can alleviate questions of access to medicines, cater to regional needs, promote country participation and improve supply.

The success of such regional pooled procurement mechanisms, however, depends on establishing good procurement procedures that are implemented through a neutral regional secretariat, transparency in demand forecasting and bargaining, and

[37] See, for example, D. DeRoeck et al., 'Regional Group Purchasing of Vaccines: Review of the Pan American Health Organization EPI Revolving Fund and the Gulf Cooperation Council Group Purchasing Program', The International Journal of Health Planning and Management 2006, https://doi.org/10.1002/hpm.822 .

[38] Note that the prices negotiated by the PAHO Revolving Fund are not publicaly available in the WHO's M14 Database, but recent discussions on the affordability of new vaccines, particularly for non-Gavi, middle-income countries, broadly suggest that while cheaper prices can result from regional pooled procurement, they are not necessarily the same as achieved under a global procurement scheme.

[39] T. Cernuschi, 'Price Transparency is a Step Toward Sustainable Access in Middle Income Countries', BMJ 2020; 368: l5375. doi: 10.1136/bmj.l5375 .

flexibility in country participation.[40] This could explain why some other programmes established for the purpose, such as a programme among Maghrebian countries in North Africa, and the Association des Centrales d'Achat des Médicaments Essentiels en Afrique (ACAME) programme in West Africa for the purchase of generic essential drugs, have not succeeded.

Other success factors include: securing political commitment from a wider range of regional buyers (to expand the financial capacity of the pooled procurement programme), greater technical cooperation in the region for health supplies, and supply chains, and the supply of essential priority products, including specific drugs and vaccines. An important issue in establishing pooled procurement models particularly for vaccines at the regional level remains that of finance. Currently a number of countries in the Asian and African regions fall under Gavi 57 (those that qualify for full support) or Gavi 64 (which includes a few countries that are in transition). The Gavi 57 supplies for vaccines are generally met by the Gavi's total vaccine funding, which is currently close to US$1 billion per annum (excluding the supply of COVID- 19 vaccines through the COVAX Facility), and this has lent the organization significant leverage to negotiate better prices with pharmaceutical companies.[41]

The 57 Gavi-eligible countries—particularly those in Africa—will continue to constitute a significant market for producers in the coming years; whether using demand in countries transitioning out of Gavi as a means to pool procurement at the regional or national level, they will have to consider the fact that outside these 57 countries, the middle-income countries in Asia, or Africa, that form part of any regional pooled procurement mechanism may have limited negotiating power simply by virtue of the limited financing capacity of such a pooled procurement mechanism. In the presence of such and other global mechanisms that currently procure drugs and vaccines, separating these (even for some products) could end up balkanizing the pooled procurement processes and thus weaken some of the current capacity to negotiate prices of drugs and vaccines from producers by reducing the total demand that these agencies cater to.[42] Conversely, even if they were to go ahead in parallel, regional procurement agencies might find it difficult to source drugs, or negotiate the same prices as global agencies with a wider reach. An interesting recent example is the joint UNICEF–PAHO tender for the procurement of COVID-19 vaccines for the PAHO region through the COVAX Facility.[43] These lessons are important to factor in as regions seek to facilitate new procurement initiatives.

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[40] Supra note 37.

[41] P. Gehl Sampath, 'Market Shaping and Market Access in the Global Vaccines Market: Approaches for the Future', 2 October 2021, https://deliverypdf.ssrn.com/delivery.php?ID=298117066081119103121001103097110009018041036079042032091098085011080090124104125110018103120097057099010080000013118072004127109075054040014107084102105071086076122095045075103091071113015075027010112001103007066100064029120010005085096006007071013104&EXT=pdf&INDEX=TRUE

[42] Ibid. See detailed discussion on pp. 16–17.

[43] UNICEF, 'UNICEF and PAHO launch joint COVID-19 vaccine tender on behalf of COVAX Facility', Press Release, 12 November 2020, https://www.unicef.org/rosa/press-releases/unicef-and-paho-launch-joint-covid-19-vaccine-tender-behalf-covax-facility .

B. Regulatory institutions

One of the most important and challenging aspects of participation in the pharmaceutical market involves the regulatory process for the approval and registration of medicines, and the oversight of production facilities and distribution. For businesses operating at a regional or global level, the commitment of personnel, technology and expense associated with regulatory compliance is typically substantial. As a practical matter, there is considerable redundancy and overlap when multiple drug regulatory authorities operating in a similar environment evaluate and monitor the same products and production facilities. For this reason, moving towards regional regulation of the pharmaceutical sector is sensible. This is based on the underlying assumption that the public using the relevant pharmaceutical products is protected at least as well as would be the case under a regime of disparate national authorities. This appears to be a reasonably sound assumption if and when a competent regional drug regulatory authority is established.

The most highly integrated and advanced regional drug regulatory authority is the European Medicines Agency (EMA). The process through which the EMA evolved is instructive for other regions contemplating integration of the drug regulatory system. When the European Union (EU) decided to move towards regional drug regulation, each Member State had its own drug regulatory authority operating under its own national regulatory regime. The EU began the integration process by gradually harmonizing the regulatory approaches used by the national authorities through a series of regional legislative enactments. Initially the central regulatory authority (the EMA) reviewed and approved few products for the EU as a whole. Cooperation among regional authorities at the scientific and technical levels was gradually enhanced, and mutual recognition of the decisions of the national drug regulators was introduced such that pharmaceutical products approved for commercial marketing in one Member State could be approved through a facilitated process in other Member States. The EMA gradually expanded the types of products that were subject to central approval. By now a large part of approval authority has been shifted to the EMA, while there is still provision for residual review by national authorities.

An important aspect of the EMA is that it is managed by an independent governing board. Drug regulatory approvals are granted by the European Commission upon recommendation of the EMA. Expert committees that review regulatory data are comprised of independent evaluators not reliant on an association with a particular Member State authority.

The EMA does not have responsibility for inspecting manufacturing facilities located within or outside the EU. Inspections and approvals are conducted by EU Member State authorities where a manufacturing facility is located, or, if abroad, by the Member State in which the importer is situated.

A takeaway from the European experience is that creating a regional drug regulatory regime is likely to involve a series of progressive steps. To facilitate cooperation and collaboration, the members of a regional arrangement should agree on the basic rules for regulatory approval. This can be done through the adoption of direct

regionwide regulations, or guidance directives to which national rules should be approximated. It should not be expected that national authorities will relinquish their roles until confidence is built in the regional institution.

Recognizing the potential advantages of establishing a regionally integrated drug regulatory authority, the African Union (AU) has established by treaty the African Medicines Agency (AMA). The AU does not have authority to adopt regulations enforceable within its Member States. As an alternative to prescribing regionwide regulation, the AU has adopted a Model Law on Medical Products Regulation that is intended to be used within national jurisdictions, with potential adaptation. The AMA is intended to foster the improvement of national regulatory authorities (NRAs) by providing technical guidance, and to help coordinate regulatory systems. At its initial stage, it does not have a central medicines approval function.

PAHO has encouraged the countries of Latin America to harmonize their regulatory schemes through the Pan American Network for Drug Regulatory Harmonization (PANDRH). Subregional integration organizations, such as Mercosur and the Andean Community, likewise encourage regulatory harmonization. To date, these efforts remain relatively modest.

In Asia, the South-East Asia Regulatory Network (SEARN) seeks to coordinate and promote regulatory harmonization in the region. Formal regional organizations such as the ASEAN Economic Community generally promote regulatory coordination and harmonization.[44]

The ASEAN region has made substantial progress in regional regulatory cooperation through, inter alia, the adoption of the ASEAN Pharmaceutical Regulatory Policy. Among the regional initiatives are the proposals for an ASEAN common technical dossier (ACTD) and the ASEAN technical requirement (ACTR).[45]

The consistent theme that emerges from efforts undertaken to date to create regional institutions for the evaluation and surveillance of pharmaceutical products is

[44] "In 2015, the PPWG started a WHO-supported project aimed at strengthening the implementation of ASEAN harmonized regulatory requirements (SIAHR). The project analyzed gaps and country-specific requirements and reported its findings to the PPWG. After thorough discussion, the PPWG decided that further action is required to address the issues. In particular, it was recognized that issues related to different implementation or interpretation of harmonized requirements are the result of several factors that can be addressed through further cooperation among NRAs, such as joint assessment of applications for marketing authorization, hands-on training, and other similar activities where staff of different NRAs can work together. PPWG also recognized that these measures require important funding and specific input from other parties such as industry and ad hoc expertise from well-resourced NRAs. On this basis, the PPWG decided to work toward the establishment of a Joint Assessment Coordinating Group (JACG) to focus on activities related to intensified collaboration among ASEAN NRAs, such as joint assessment of applications for marketing authorization and similar activities where staff of different NRAs can work together,
respecting national decision-making processes." (Ahmad, R. et al., 'Joint Assessment of Marketing Authorization Applications: Cooperation Among ASEAN Drug Regulatory Authorities', DIA Global Forum, September 2021, https://globalforum.diaglobal.org/issue/september-2021/joint-assessment-of-marketing-authorization-applications-cooperation-among-asean-drug-regulatory-authorities/

[45] ASEAN, supra note 35.

that governments begin by seeking to harmonize or approximate national legislation and procedures among the participating countries of the region. This is so that each of the national regulatory authorities approaches approvals in the same way. This facilitates sharing and use of relevant information across borders. The next step may be some form of mutual recognition such that work undertaken by one regulatory authority can be relied on by another, thereby accelerating the process of acceptance and entry into the market. A third step or phase may be reliance on a central drug regulatory authority whose approvals are used throughout the region. The central regional authority could be designed in a variety of ways. For example, it could either establish and maintain its own laboratory and testing facilities (and personnel to operate them), or it could entrust a national authority within the region with carrying out aspects of evaluation. As evidenced by practice in the EU, the central authority might gradually expand the scope of products that it evaluates on behalf of the entire regional arrangement.

A key element is that the central regulatory authority should be viewed as a neutral scientific entity, and not operating on behalf of any particular Member State of the regional organization.

It is important also to acknowledge that addressing the concerns of health professionals in terms of their employment and functions is essential to build regional pharmaceutical regulatory institutions. Provisions must be made for transitioning staff at national levels to working in a regional capacity in a way that preserves the interests of professional staff.

For some regions, such as Africa, simultaneously undertaking regulatory system strengthening and regulatory harmonization poses significant challenges. WHO conducts evaluations of NRAs to assess the overall 'maturity' of the regulatory system on a scale of 1 (existence of some elements of regulatory system) to 4 (operating at advanced level of performance and continuous improvement).[46] There is currently only a handful of NRAs in LMICs that have reached Maturity Level 3 (which confirms that a stable, well-functioning regulatory system is in place),[47] although a number – such as in Ghana – are in the process of improvements to reach Maturity Level 4. Regulatory harmonization, associated with some consideration of 'regional' market approvals, and processes that facilitate region wide registration could help alleviate some of these hurdles. This could also include mutual recognition agreements and reliance on third-country drug regulatory authority decisions by more 'stringent regulatory regimes' and/or the WHO.

Another critical regulatory function is inspection and approval of manufacturing facilities. This involves inspection for conformity with Good Manufacturing Practices (GMP). Different countries and regions may use somewhat different approaches to GMP. If a regional hub is intending to also export to third countries or regions, and/or to sell to international procurement authorities, a stringent standard of GMP is likely to facilitate that. It may be necessary in some cases.

[46] https://www.who.int/tools/global-benchmarking-tools
[47] https://cdn.who.int/media/docs/default-source/medicines/regulatory-systems/list-of-nras-operating-at-ml3-and-ml4.v2.pdf?sfvrsn=ee93064f_6&download=true

C. Policy coordination

The successful establishment of a regional hub should be undertaken in coordination with the adaptation of other policy measures. For a region in which tariffs and quotas have been effectively eliminated among parties to a regional arrangement (customs union or free trade area), this adaptation should already have taken place in respect of those measures. Moreover, since exports and imports within the region should be treated preferentially to imports from outside the region, it should be possible to maintain tariffs that provide some protection to the finished products of the regional hub. Caution must be exercised, however, with respect to imports of component materials that are not or cannot otherwise be sourced within the region, since tariffs have the effect of raising the cost of the final products.

Just as a region may find it helpful to establish a common drug regulatory authority, so it is important to coordinate the regulatory requirements within national borders, including on matters such as packaging and labelling. Offering easy registration for local companies (through a one-stop process) and providing policy incentives for better coordination between R&D institutions, university centres of excellence and private companies that are in the clustered areas will also be extremely important for continued investment in production, innovation and eventual R&D.

An important question for regional hubs is the applicable regime for taxation. Presumably, each country of the region that participates in the creation of the hub will be interested in a share of whatever taxes may be paid by the hub's owner/operator, given the co-investment element in such a hub. The ideal situation would be to constitute the regional hub as a taxation-free zone to give the producer an advantage over competitors. This, however, needs to be balanced with the interests of established producers within the region, with a view to creating a scheme for taxation and sharing of revenues that creates a level playing field within the region.

D. Financing

The mechanism for financing the establishment of a regional pharmaceutical hub will depend on how the ownership structure is organized, but will entail a significant amount of public investment at the national or regional level. If the idea is to establish an area that will attract private investors that will create privately owned and operated manufacturing facilities, the governments of the region should agree on an incentive package that would induce investment, and potentially focus on facilitating infrastructure through public budget. Another option would be for the governments to co-invest in or entirely own some of the manufacturing facilities. If a decision is made to establish government-owned manufacturing facilities, financing issues will be different. A principal question will then be how governments will apportion contributions, and what interest in the regional hub facilities will be allocated in return.

Part of this equation in either case, as discussed earlier, will involve procurement or buy-back or offtake guarantees. It may also be important to identify potential larger-scale lending institutions capable of offering globally competitive rates of interest,

recalling that private pharmaceutical companies in Africa, for example, sometimes find it difficult to borrow at globally competitive interest rates.

E. Technology

Access to technology will be a key element of any regional pharmaceutical hub effort. There are substantial issues to be addressed from two different perspectives. From an external sourcing perspective, the questions of what kinds of technology should be sourced from outside, and through which channels, remain essential. This needs to be matched by an exploration of whether there is sufficient technology absorption capacity in the region, and if not, what kinds of regional R&D, skills and other training are needed to enable the region to benefit, and build on, externally sourced technological inputs. One approach would be to encourage foreign direct investment, including joint venture investment, in the hub, with the inclusion of the technology component as part of the investment package. This is the traditional or conventional mechanism for securing access to more advanced technologies, and has been followed by a number of emerging economies in several sectors in the past. Such technology transfer, it should be expected, will build on technology already present within the region for R&D, process and product innovation, and production.

Alternatively, enterprises within a regional hub could seek to license technology from enterprises outside the region. However, owners of patents and trade secrets on advanced pharmaceutical technologies are typically reluctant to license that technology to unrelated third parties. A significant governance issue for the design of the regional hub would be to structure close linkages between the production hub and the R&D institutes already engaged in similar technology specialization in the region. Integrating local skills and personnel as much as possible into ongoing regional production will ensure better ecosystem linkages.

As with a traditional resource-pooling arrangement, such as a patent pool, a major issue with respect to a regional hub is whether it can create such a regional patent pool of relevant technologies, and how its governance will be undertaken. In principle, a regional hub could be subject to the laws and jurisdiction of the country in which it is located, and its management could be governed by whatever enterprise management rules are enforce in that jurisdiction. Even if that is the case, if the regional hub is going to serve as the production and distribution platform for a group of countries, that group will want a voice in the management of the hub.

The need to continuously develop and provide access to technologies relevant to producing and distributing pharmaceutical products is of great importance to the prospects for successful regionalization of local production. There are well-understood alternative mechanisms for addressing technology requirements, including both public- and private-sector approaches, voluntary and/or involuntary transfer mechanisms, and a variety of potential industry structural configurations. Annex 1 to this paper discusses some of these avenues.

F. Market coordination and consolidation

The models discussed in the paper can have different impacts on the market structure. For example, establishing a planned distributed supply model (section 3.3) would create a risk of placing pricing power in the hands of the designated producers. In that instance, there are at least two potential ways to address this concentration. One is to have prices and volumes determined by a regional authority, including through the establishment of contractual advance purchase commitments. The second would be to establish price preferences in favour of the designated producers, but allow imports from alternative (presumably foreign) sources in the event that prices of the designated supplier exceed the competitive import prices by a certain amount (e.g. the price from the designated supplier must be within 10–15 percent of the potential import price).

Similarly, establishing a regional hub with a primary local producer begs the question of competition from other local and international producers. Choosing specific firms for production is always tricky, from an economic perspective, given that it could create an unfair advantage for one/some firms over others. How countries manage this, through industrial and competition policy, will become highly relevant.

As with the regional hub model, the distributed supply chain model presupposes a political/industrial policy decision-making structure to perform the allocative function for production and for product procurement/pricing. That could be done through an existing regional arrangement decision-making structure, or through a self-standing agreement among the participating countries. But its success will rely on close monitoring of market dynamics and policy coordination.

G. Taxation and spending

A critical element of the global constitutive structure in which the nation State plays the central role has to do with taxation and spending. Governments are typically dependent on payment of taxes by individuals and businesses for their resources, and have the authority to spend or allocate those resources. Import tariffs, among other trade-related fees and charges, are a form of taxation ultimately subject to spending or allocation by the national government, or by subunits according to the relevant constitution.

5. Coordinating regional production: Some concluding thoughts

Public or governmental decision-making may take place at multiple levels: municipal, state/provincial, national, regional or multilateral/plurilateral. Decision-making within a nation is governed by a constitutional framework that ascribes functions to institutions, and establishes a hierarchy of authority among those institutions and the rules or laws they may promulgate. Comparative constitutional law reveals a significant variation among governance ‘formulas’. But, notwithstanding differences in internal constitutional specifics, there is a widely shared understanding among the world community that national governments have the authority to control activities

within their national territory. This is reflected in the structure of the United Nations, the members of which are nation States.[48]

These fundamental features of global governmental organization help to explain why the successful establishment of regional organizations with effective governance features is difficult. National governments that ordinarily exercise plenary power within their territories are deciding to share that power with other governments, including regional governance institutions. In principle, foreign governments and regional institutions assume the authority under the defined conditions of the regional charter to make decisions that bind the national governments within the regional sphere of authority. This realignment of power has effects within the nations of the region, including the internal 'popular' and business constituencies on which the government depends for support.

For a successful realignment of power on a regional basis to take place, each national government and its internal constituency must conclude that the nation State will be 'better off', or at least 'not worse off'. Otherwise, the incentive for cooperation is lacking. Of course, this does not mean that each constituency within each nation must conclude that it will be at least 'no worse off', because in the economic sphere government decision-making may benefit some constituencies and create negative consequences for others. But each government must presumably conclude that 'on the whole' the nation will be better served by an arrangement such that it can withstand contrary pressure from internal constituents.

This helps explain why establishing effective regional governance structures is very difficult. If decision making is other than by 'consensus', an individual nation may find that it is subject to a decision which it evaluates to make it worse off. Although such a 'negative' decision might be acceptable on a limited basis on the theory that the allocation of benefits will balance out, a consistent perception by a particular nation in a regional group that it is suffering from group decisions will create friction and ultimately some form of dissolution.

For some multilateral organizations, a major case in point being the World Trade Organization, decision making is by consensus, and this avoids the problem of the unwilling 'worse off' member. But it is by today evident that all-encompassing consensus governance can be very inefficient and perhaps ultimately unworkable.

Perhaps the most studied example of non-consensus regional decision-making is the framework of the EU, which among regional organizations probably comes closest to a 'quasi-federal' polity. The EU has gone through a long period of constitutional and institutional evolution, dating back to the late 1950s. It has proceeded from concentration of power in a Council of Ministers representing Member States, to a distribution of power between the Council of Ministers and the European Parliament. For the most sensitive matters, consensus is required in the Council of Ministers along with approval of the Parliament. But for most matters, a complex system of

[48] The EU, by way of illustration, is not a 'member' of the United Nations, but rather an observer. See, for example, United Nations Regional Information Centre for Western Europe, 'How the European Union and the United Nations cooperate', Bonn, Germany, 2021, https://unric.org/en/wp-content/uploads/sites/15/2021/02/Leporello_EU-VN_e.pdf

‘qualified majority voting’ weights the authority of the Member States within the Council, allowing effective ‘less than consensus’ decision-making, also balanced by varying voting requirements in the Parliament. There is also very substantial delegation of implementing authority to the European Commission, and oversight by the Court of Justice of the European Union. And yet, with this ‘evolved’ system of regional constitutive governance, an important member of the EU withdrew on the basis of ‘popular dissatisfaction’ with EU governance.

The AU and the newly constituted AfCFTA each have their own governance structures, although the two regional organizations are closely related. At the conceptual level, establishing a local pharmaceutical production base for the African continent is part of the AU agenda, incluidng through the African Union Development Agency (AUDA-NEPAD)[49] The AfCTFA should play an important role in the creation of a regionwide local pharmaceutical production base by facilitating trade. AUDA-NEPAD developed a Pharmaceutical Manufacturing Plan for Africa ‘endorsed’ by the AU Heads of State in 2007[50] but this Plan has not been implemented and by now is dated.

This leads to the question, assuming arguendo, that African governments, presumably through a high-level political body at the AU, conclude that developing and implementing a detailed programme for pharmaceutical manufacturing within Africa is a priority, how would decision-making regarding the overall structure and details of the plan be carried out? Would it be done within one of the existing institutional structures established by the AU Constitutive Act and its underlying institutional evolution? Would it be done within the framework of the AfCFTA? Or would it be necessary or useful to establish a self-standing regional agreement addressing development, manufacturing and distribution of pharmaceuticals? Within any of those potential constitutive frameworks, how will decision-making be carried out? Could decision-making be undertaken by consensus among 54 countries or whatever size group participates? Would it be better to envisage a series of subregions within Africa where 10 or 12 countries participate?

According to the World Trade Organization Regional Trade Agreements (RTAs) Database, there are over 350 active RTAs in force, with a wide geographic distribution.[51] Even considering that this number includes certain overlaps, and so forth, suffice it to say there are ‘many’ regional arrangements in force today, with a wide variety of institutional arrangements. These vary in terms of integration depth along a number of axes, ranging from a high level of political integration, as in the EU, to much more modest forms of institutional authority, as embodied, by way of example, in the US–Mexico–Canada Agreement (USMCA). With respect to the low level of integrated political decision-making authority embodied in the USMCA, there is no ‘regional institution’ with authority to make decisions such as would allocate production responsibility for pharmaceuticals across the region. This would require a supplemental agreement of some type.

[49] See NEPAD Home | AUDA-NEPAD.
[50] African Union Development Agency, ‘Pharmaceutical Manufacturing Plan for Africa’, Accra, Ghana, 2007, https://www.nepad.org/publication/pharmaceutical-manufacturing-plan-africa.
[51] See http://rtais.wto.org/UI/PublicMaintainRTAHome.aspx.

In short, putting aside the EU, there is probably no regional arrangement presently constituted whose political institutions have existing authority to create and implement a regionwide industrial policy such as might allocate responsibility for producing pharmaceuticals to a particular member country, or to establish a regional production hub designated to supply the region. For this reason, in almost all cases we would envisage that the establishment of some 'stronger form' of agreement to establish a regional production framework would require a self-standing agreement to be negotiated among the country parties.

We envisage that the next phase of this project will entail discussion with interested parties in their respective regions regarding how a self-standing agreement regarding the establishment of regional production might be designed, including its relevant industrial policy elements and its public health elements. Both Asian and African regions have several initiatives under way that make them well poised for such discussions in the immediate future. The political constellations and constitutive/legal frameworks may be similar for diverse regions, but they may also be quite different. Although it might be possible to generate a model agreement that would be equally useful for different geographic regions, more likely this next phase should be approached on a region-to-region basis, rather than by aiming for a single model.

Implicit throughout this paper is an assumption that bolstering regional capacity to develop, produce and distribute pharmaceutical products will improve the conditions of access for those needing those products. Because R&D efforts and the build-up of production and distribution capacity take time, benefits for health systems and medicines users may not manifest themselves immediately. Participating governments and other stakeholders should not view regionalization of local production as an immediate fix for supply and access constraints. The medium- to longer-term benefits in terms of security of supply, and improvements in the R&D, regulatory and infrastructure environments, should achieve the ultimate aim of improving the health of those living within the region.

Annex 1: Technology transfer

Technology pooling and technology transfer at the regional level

A looming question is whether a regional hub would seek to take advantage of the possibilities for government use and/or compulsory licensing of patents, and use of prior regulatory submissions for the approval of products. Government use and/or compulsory licensing presupposes a political commitment among the governments participating in the regional hub to withstand political pressure that will be placed on them from the home countries of originator companies. However, it is important to note that the practice of compulsory licensing is recognized and incorporated as an option in the World Trade Organization's TRIPS Agreement. In addition, the least developed countries have the option not to enforce patents or regulatory marketing exclusivity, providing a significant potential advantage for the location of a regional hub. This would not, however, overcome such protections in importing countries without actions to overcome patents taken by those countries.

The governments of the region might decide to establish a technology pool from which enterprises in the region could draw to establish local production facilities, or even to pursue additional research. Such a pool could be established on either a voluntary or a non-voluntary (compulsory) basis. Some technology owners have already agreed to make their technology available under licence through the mechanism of the Medicines Patent Pool (MPP). Nevertheless, the role of the MPP remains somewhat limited (e.g., in the area of vaccines), and the alternative of a non-voluntary arrangement could also be pursued.

The idea of establishing a regional technology pool based on compulsory licensing (including government use) of patents does not presuppose that technology owners will not be adequately compensated. The TRIPS Agreement recognizes the principle of adequate remuneration in the circumstances of the case. Moreover, one of the underlying objectives of establishing a pool of technology to which the owners of the technology must contribute may not be so much as to have the benefits of the products of the technology (at least in many cases, in the short run), but to gain greater voice or control over how the products are distributed.[52] During the COVID-19 pandemic, while concerns were indeed raised regarding access to underlying technologies, equivalent concerns were raised with decision-making regarding the allocation of products (e.g. vaccines), with decision-making left largely in the hands of private enterprises and government purchasers. A technology pool could be beneficial to promote a more equitable allocation of the products of technology.

Whether compulsory licensing is used may ultimately depend on the willingness of technology owners to voluntarily license their technology. The establishment of regional procurement facilities and the creation of bulk purchasing on a regional basis might well provide the push that is needed to induce perspective technology licensees to make technology transfer commitments, or at least agree to reduce prices and speed up deliveries, to avoid losing control over how production is undertaken and allocated. Regional procurement arrangements would provide leverage for the participating governments in various ways.[53]

[52] See, for example, F.M. Abbott and J.H. Reichman, 'Facilitating Access to Cross-Border Supplies of Patented Pharmaceuticals: The Case of the COVID-19 Pandemic', *Journal of International Economic Law (Oxford)* 2020; 23(3): 535–561.
[53] Ibid.

Technology transfer and licensing terms

Although the conditions under which licensing is undertaken may vary, it will nevertheless be necessary to establish the terms and conditions under which licences are executed. Whether licensing is undertaken along a vertical chain within a single country or region, or takes place through in-licensing from parties outside a country or region, there are many variables that are addressed in technology licensing/transfer agreements. They include:

- Defining the specific subject matter of the licence, such as patents (of various types),
- trademarks, copyrights, trade secrets and other information/data (including regulatory data),designs, etc.
- Will the licence and technology transfer be exclusive to the licensee, or may it be licensed to and used by other parties (including the licensor)? This will be particularly important in a hub where a number of nodes are anticipated.
- Does the licence permit sales of resulting products worldwide or to a limited geography, or to a limited set of purchasers?
- Which party is allowed to make use of improvements to the technology? And how are the rights over these improvements allocated
- Is technical training/know-how transfer included within the scope of the licensing agreement? And for what length of time?
- What is the compensation arrangement between the licensor and licensee?
- The compensation arrangement between joint venture partners, on the one hand, and arm's length parties may be substantially different.
- Will there be minimum sales or compensation under the licence to maintain it in force?
- Will there be controls on the prices of products produced under the arrangement?
- Which party will be responsible for liabilities either from conflicts with other intellectual
- property owners or from injuries that may occur from use of the technology?
- What will be the currency used for payment, and which party will be responsible for payment of relevant taxes?
- In the health technology sector, will the licensor have an obligation to supply regulatory data and/or participate in securing marketing approval for the products?
- What will be the term or duration of the licence? May it be sublicensed, and through what process? What happens in the event of a default by either party?
- How will disputes be resolved? Which law will govern?
- What will be the provisions for reporting and auditing under the arrangement?
- Will the terms of the licensing arrangement be disclosed, and to whom?

For joint venture arrangements, there are a substantial number of decisions to be made concerning structure:

- Will a governmental authority review (and approve/disapprove) the terms of the joint venture, and according to what criteria?
- What will be the respective ownership percentages
- How will ‘in-kind’ contributions, such as transfer of technology, be valued?
- How will decision-making be undertaken?
- Are the parties entitled to sell or transfer their interests?
- Will there be conditions on the nationality or type of owner (e.g. public or private)?
- How will the proceeds of the joint venture be distributed (or retained and reinvested)?
- What will happen to the assets of the joint venture in the event of dissolution?
- How will disputes be resolved?