Realistic ambitions

Technology transfer for biologics platform technologies

CHAPTER 10

Realistic Ambitions: Technology Transfer for Biologics Platform Technologies

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Introduction

Covid-19 disrupted vaccine, drugs and diagnostics supply chains and exposed African countries' epidemic and pandemic unpreparedness (Chapter 2). These events called for new sociotechnical imaginaries of local production to improve local health security and cumulatively assure global health security. This in turn requires collaboration between the state, technocrats, advocacy actors and the public to generate and sustain

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long-term legitimacy, agency and urgency for resource allocation to the local health-industry complex development.

Building on existing technological capabilities in the local industry is an important first step to enhancing local health industries, including local production of oncology drugs in East Africa (Chapters 7 and 8). The next step is local production of more complex cancer therapies such as monoclonal antibodies (MAbs), which entails building a vibrant biologics industry. We take a contrarian position to choruses of "Africa should focus on the low-tech therapies" that we have heard in workshops and conferences, and ask why should African entrepreneurs not advance and compete internationally? There is an urgent need to build a robust local biopharmaceutical manufacturing ecosystem and to create advanced local health-industry complexes that generate better health outcomes for cancer and other patients. Production of advanced therapies is not the sole preserve of high-income countries. Covid-19 showed us the folly of such technology and innovation expertise exceptionalism for certain regions of the world.

We liken Covid-19 to a volcano: a *fast moving disaster* which creates an immediate crisis and quickly galvanises political agency and urgency to change public policy. However, there are also *slow moving but hugely impactful disasters* analogous to a glacier. Cancer and other non-communicable diseases affect many people on the continent and deserve the same urgent response and action as infectious diseases. Announcing technology transfer for mRNA vaccines to six African countries the WHO Director General said, "The best way to address health emergencies and reach universal health coverage is to significantly increase the capacity of all regions to manufacture the health products they need."[1]

This vision of an Africa with an advanced local health–industry complex also emerged from interviews with African industrialists and healthcare respondents. Biologics including regenerative medicine, gene therapy and MAbs are still expensive to produce and to procure for healthcare systems even in wealthy countries. However, with the right investment in technological capabilities, sustained learning and market formation they can be localised in Africa. In this chapter, we focus on biosimilars for MAbs because a significant number of them have fallen off-patent. The "generic" versions of biologics are called biosimilars. They provide an opportunity for technological capability upgrading and learning. For current drug manufacturers on the continent, biosimilars are a disruptive innovation, bringing significant discontinuities in production,

quality assurance, distribution, industry-clinical linkages and regulatory processes.

Employing the concepts of disruptive and incremental innovation, we argue that technology transfer for MAbs is not insurmountable. For vaccine manufacturers, biologics are an incremental innovation because they already possess relevant sets of skills and capabilities. However, for regulators conversant with chemical drugs, biologics will be a disruptive innovation. Health system financing and procurement will need to be designed to adequately compensate local biologics (MAbs) manufacturers in a way that ensures business profitability and sustainability; this is the remit of innovative procurement (Chataway et al., 2016).

Why are Biologics, Especially MAbs, Important for African Countries?

We proffer three reasons why biologics and particularly MAbs are important for African countries: they open up international business opportunities, broaden technology choices and offer opportunities for value chain and technological capabilities upgrading.

Biopharmaceuticals are big business, and African entrepreneurs should participate in that market. Global expenditure on biopharmaceuticals was USD 277 billion in 2017 and is forecast to reach USD452 billion by 2022 (Cun et al., 2021). MAbs are expected to generate revenues of USD 300 billion by 2025 driven by their utility in immune-diagnosis and immunotherapy (El Abd et al., 2022). The sector is set to expand because it holds immense promise for many currently "undruggable" diseases. Biologics, specifically MAbs and RNA (ribonucleic acid) therapeutics are expected to address diseases caused by a broad range of pathogens that include group A and B *Streptococcus*, parasites such as *Taxoplasma gondii*, bacterial infections, cancer (colon carcinoma and melanoma) and passive vaccination (Blakney et al., 2021). It is these yet unrealised business promises of a vibrant emerging sector that have generated heated debates on strict observance of IP (intellectual property) even during the Covid-19 pandemic. When developing countries tried to reverse engineer mRNA vaccines, there was active resistance from incumbent firms. The recent refusal by innovator companies to share Covid19 mRNA vaccines technology openly with developing countries[2] (UNAIDS, 2021), which has caused outrage (Malpani & Maitland, 2021)

may be premised on their fear of losing future lucrative oncology biopharmaceutical markets. Hence, the aggressive strategies to protect the first mover's advantage, driven by the blockbuster business model, even in the face of humanitarian need in African countries during Covid19.

Strong local health security is the foundation for robust global health security (Chapter 1). Localising biologics manufacture reduces current concentration risks. It contributes to enhanced global redistributed manufacturing systems for healthcare, by moving production facilities closer to point of care and embedding better demand signalling. The result should be better health outcomes.

Biological therapeutics play an important role in cancer therapies, and compared to chemical drugs, are reputed to have reduced side effects. Morrow and Felcone (2004) broadly categorise biologic agents as hormones (growth hormone, insulin or parathyroid hormone), interleukins, interferons, MAb, Growth Factors, proteins, polypeptides and vaccines. MAbs have grown as an important cancer therapy targeting particular types of cancers (Table 10.1). Recently regenerative medicine (especially immunotherapies) has emerged as a promising cancer therapy. Biologics technology transfer could drastically improve health outcomes for cancer patients by reducing treatment cost in the medium term, improving supply response and making the therapies more available. The Covid19 crisis triggered important questioning of conventional wisdom of dependency on global health supply chains especially during pandemics. Endemic and non-communicable disease are causing havoc and deserve the same urgency and agency to solve them as the pandemic effort.

Table 10.1 Monoclonal antibody therapies and targeted cancers

Monoclonal antibody	*Targeted cancer(s)*
Ipilimumab	Melanoma
Trastuzumab	Breast cancer
Panitumumab	Colon and rectal cancer
Alemtuzumab	Lymphocytic leukaemia
Cetuximab	Colon and rectal cancer; Head and neck cancer
Rituximab	Non-Hodgkinson's lymphoma

Source Compiled by authors from secondary sources

RNA-based therapeutics are another class of promising remedies for cancer and other infectious diseases. Current clinical trials of RNA therapeutics reveal application across a broad range of diseases including cystic fibrosis, neuroendocrine tumours, glaucoma, age-related macular degeneration, hepatic fibrosis, idiopathic pulmonary fibrosis and chronic hepatitis B viral infection (Dammes & Peer, 2020). Another class of biologics with great potential but still in infancy are cell therapies. Even for these, the business models, process technologies and regulatory systems are still in development in high-income economies (Banda et al., 2018, 2019). However, there is no reason why LMICs could not develop these therapeutics through more cost-effective manufacturing and delivery methods. The foundational technology and skills for these emerging technologies are similar to those found in the vaccine manufacturing sector, research institutions and universities.

Incremental Versus Disruptive Innovation and Impact on Business Models

Chapter 7 distinguished product innovations, which include physical artefacts or services that are new or possess significant improvements, from process innovations such as improved production techniques or delivery methods. Product innovations, including enhanced sub-units or components, software or attributes that embody better functionalities may be new to the world or, more usually, new to a certain place. The OECD[3] also identifies marketing innovations, such as better product design, product promotion or pricing and organisational innovations that enhance performance.

Process and product innovations can be disruptive or incremental in given industrial contexts. Tait et al., (2018) applied these concepts to new-to-the-world innovations that included cell therapies, financial technologies (FinTech) and synthetic biology. Their disruptive/incremental distinction is based on the impact of the innovation on business models, ability to generate competitive advantage, impact on the environment, how they relate to pre-existing regulatory frameworks, and whether they lead to sectoral transformations thereby generating stakeholder/citizen concerns. Disruptive innovations are characterised by discontinuities in innovation pathways, requiring new areas of R&D and creating new modes of production and markets. For example, FinTech such as mobile money in African countries brought about new business models.

Mobile telephony companies and not banks introduced mobile money, and because of automation and resultant reduction in transaction costs, mobile money attracted previously unbanked populations and eventually eroded the market base of traditional banks. However, countries struggled with regulating mobile money because the business model was embedded in mobile phone companies, which did not fall under the regulatory purview of the central banks. Thus, mobile money was a disruptive innovation for traditional banks and the regulator. Disruptive innovations thus cause sectoral transformations and establish new sectors. These may have no regulatory precedent, hence the regulatory challenges described above. Such disruptive innovations may need new production or delivery modes, which necessitate the creation of new value chains.

Incremental innovations on the other hand are characterised by small improvements in products and processes, and consequently fit well with a firm's current business model(s). They usually lead to competitive advantages but align well with pre-existing regulatory frameworks. Therefore, incremental innovations do not usually generate sectoral transformations or cause significant stakeholder/citizen concerns or oppositions (ibid). Slow-release drugs were an incremental innovation over ordinary drugs. The methods of production, quality control and storage and distribution were essentially the same. Thus, incumbent companies could easily shift to new production lines as the skills, equipment and processes were similar. Table 10.2 describes the different impact of disruptive and incremental innovation on innovation pathways, research and development (R&D), competitive advantage generation, applicability of existing value chains or the need to develop new ones, and impact on regulatory capabilities and frameworks under which they fall.

Local manufacturing of MAbs in countries without vaccine manufacturing capabilities will be a disruptive innovation. There are, however, African countries in North Africa that already produce MAbs. Technology was successfully transferred from Israel and Russia amongst others. For current non-vaccine manufacturers the disruption emanates from the different skills sets, biological nature of starting materials, subsequent idiosyncrasies of production and distribution processes, quality assurance as well as regulatory and governance systems. For vaccine manufacturers the converse is true, and they are the best starting point for MAbs technology transfer. However, technology transfer is not an easy process, given current technological, infrastructural and institutional realities. In spite of this, countries can systematically build and broaden

Table 10.2 Impact of disruptive and incremental innovation on business models, value chains and processes

Disruptive innovation	*Incremental innovation*
Discontinuities in innovation pathways	Small incremental changes in innovation pathways
Requires new areas of R&D	Builds on existing R&D capabilities and skills
Creates new methods of production and markets	Generates competitive advantage by more efficient approaches to production and markets
May require new value chains or new roles in existing value chains	Likely to easily modify existing value chains and actors involved
Can create entirely new sectors with societal and economic benefits	Likely to build on existing sectors with the possibility of economic and societal benefit
Given the factors above—likely to lead to sectoral transformation and displacement of incumbent actors	Not likely to lead to sectoral transformation given the abovementioned factors
No regulatory precedence to govern potential human and environmental risk and safety issues	Likely to be covered by existing regulatory systems
Could lead to stakeholder concerns given no obvious regulatory system with a track record of success	Unlikely to lead to stakeholder concerns given there is an existing regulatory system with a track record of application
There may be a need to create a new business model if the innovation and technology and pathways to market do not exist	Existing business models are capable of incorporating the new innovation or technology

Source Compiled by authors from Tait et al. (2018)

industrial and technological bases coupled with systematic support for entrepreneurship. Incremental innovation provides a conceptual framework for constructing pragmatic technological, policy and practice interventions that can support the development of the biologics sector. The attraction of the incremental innovation framework is its ability to explain why it has been possible to transfer rapidly Covid19 vaccine technology to current African vaccine manufacturing entities. The framework provides a basis for arguing for resource allocation, and extension of long-term technology transfer, to emerging biologics such as RNA therapeutics for oncology needs and other currently "undruggable" diseases.

African Vaccine Manufacturing Footprint—Where are We Starting from?

Vaccine manufacturing is not a new phenomenon on the continent. Currently four countries have vaccine manufacturing capabilities; Egypt, Tunisia, Senegal and South Africa (Chapter 1; details in Table 10.3). Vacsera in Egypt was originally set up as a small government laboratory in 1897. It produces Tetanus Toxoid, Diphtheria and Tetanus Toxoid, Diphtheria, Tetanus and Pertussis, Meningococcal, Cholera and Typhoid vaccines. Demonstrating the incremental nature of vaccines, by February 2022, Vacsera was reported[4] to be producing over 30 million doses of the Sinovac/Vacsera Covid-19 vaccine. Sinovac Biotech transferred the mRNA technology to Vacsera. Egypt, Tunisia, Kenya, Nigeria, Senegal and South Africa are part of the WHO consortium that will engage in mRNA vaccine technology transfer.[5]

In Tunisia, Institut Pasteur de Tunis was established in 1893 and it produces the BCG and rabies vaccines. Senegal's Institut Pasteur de Dakar established in 1896 is one of four WHO-pre-qualified manufacturers of yellow fever vaccine (Ampofo, 2021). In July 2021, the Republic of Senegal working with Team Europe agreed to build a Covid19 and other endemic disease vaccine manufacturing plant in Senegal.[6] In addition, the Institut Pasteur de Dakar will host the regional manufacturing hub. The main hub funder is Team Europe, which with the Senegalese government will co-fund the plant's establishment. Team Europe is comprised of EU institutions including the European Investment Bank, the EU, its member states, and the European Bank for Reconstruction and Development (EBRD) (Keijzer et al., 2021).

South Africa has made huge strides in biologics manufacture. Institutions involved in biologics manufacture date back to the 1950s, although Aspen began in the 1850s in other drug businesses. Prominent companies on the biologics terrain include Afrigen Biologics, Biovac, Aspen and Cape Biopharms amongst others (Table 10.3).

Vaccine manufacturing plants in Senegal, Tunisia and Egypt are state owned, and South Africa has a public–private partnership, Biovac, plus CapeBiopharm, Aspen and Afrigen Biologics, which are private companies. Although Ethiopia, Nigeria, Zimbabwe and Ghana do not at the time of writing have vaccine manufacturing plants, they have long had an interest in establishing local vaccine production as members of the

Table 10.3 Vaccine and biologics manufacturers and the products manufactured locally as at 2022

Country	*Organisation*	*Established*	*Vaccines manufactured*
Egypt	Vacsera The only producer of vaccines and sera and one of the main blood banks	1897	• Tetanus Toxoid Vaccine • Diphtheria and Tetanus Toxoid Vaccine [paediatric and adult use] • Diphtheria, Tetanus and Pertussis • Meningococcal Vaccine • Cholera Vaccine • Typhoid Vaccine Produces Sinovac vaccines. Technology transfer between China's Sinovac and Vacsera A new vaccine facility outside Cairo will have capacity for 1 billion doses per annum Egypt is a participant on the WHO programme to transfer mRNA vaccine technology
Senegal	Institut Pasteur de Dakar "A non-profit association for public utility"[7] with over 80 years of vaccine production	1896	• Yellow Fever—since 1930s One of four WHO approved manufactures of Yellow Fever vaccine in the world
South Africa	Aspen	1850 went public in 1997[8]	• Johnson and Johnson Covid-19 Vaccine. First Covid vaccines manufactured on the continent. (Fill and Finish)

(continued)

Table 10.3 (continued)

Country	*Organisation*	*Established*	*Vaccines manufactured*
	Biovac	2003 as a PPP but has long links to previous vaccine manufacturing initiatives in South Africa	• BCG for TB • Measles Vaccine • Pneumococcal Conjugate Vaccine • Hepatitis B Vaccine • Hexavalent Vaccine for *Diphteria, Tetanus, Pertussi, Poliomyelitis, Haemophilus influenza B and Hepatitis B* • Tetanus Toxoid Vaccine Agreement to produce Pfizer Covid19 vaccine [Fill and Finish] Group B Streptococcus (GBS) Vaccine Development
	Cape Biopharms. Spun-off from The University of Cape Town's Biopharm Research Unit	2018	Production of recombinant proteins in tobacco plants Plant-based transient expression Molecular pharming (recombinant expression of pharmaceutically useful proteins in plants as bioreactors) (Marsian and Lomonossof, 2016)
	Afrigen Biologics	2014	Encapsulation technologies Vaccine adjuvants
Tunisia	Institut Pasteur de Tunis	1893-commissioning of establishment	• BCG Vaccines—Intradermal BCG and fresh BCG for Immunotherapy [bladder tumours] Under development—rabies vaccines for human and veterinary use and bacterial vaccines for veterinary use (mixed anthrax and enterotoxemia)

Source Compiled from Banda et al. (2022)

African Vaccine Manufacturing Initiative. Kenya has established Biovax, using KEMRI Production Unit as its stepping-stone (Chapter 2).

Underscoring the incremental innovation argument and technological readiness, Vacsera successfully transferred technology from China to produce Sinovac Covid vaccines, whilst Aspen in South Africa quickly transferred technology for Johnson and Johnson's Covid19 vaccines. Biovac agreed to fill-finish the Pfizer Covid19 vaccine. Morocco was already producing 3 million doses of the Chinese anti-Covid Sinopharm vaccine as at January 2022. This is evidence that new biologics are an incremental innovation for existing vaccine manufacturers, and technology transfer is possible. Contrary to this clear demonstration of technology transfer, some commentators in interviews, workshops and conferences argued that these technologies are too complex, requiring advanced processing technology and technical skills, and therefore technology transfer to developing countries is too difficult. They argue that African countries should either procure finished products or engage in fill and finish operations based on modular designs exported from incumbents. We argue to the contrary, that the requisite skills and capabilities exist for technology transfer and accept that more technological learning is required.

African countries, in conjunction with the WHO, have ignored these negative arguments and reverse engineered the mRNA vaccine technology in South Africa, using freely available information and solidarity from international scientists. The initiative involved using current vaccine manufacturers as centres for technology transfer. The consortium consists of Afrigen Biologics, Biovac with support from WHO, Medicine Patent Pool, South African Medical Research Council and African Centres for Disease Control. It is a component of the broader African Vaccine Manufacturing project set up in April 2021 at the height of vaccine nationalism. In January 2022 the South African company, Afrigen Biologics successfully reverse engineered Moderna's Covid19 vaccine, "both the mRNA and the formulation" and was at the time of writing optimising cheaper formulations that do not require refrigeration (Davies, 2022). Davies (2022) reports that these efforts were being undermined, and alternatives proposed were that modular-based mRNA factories from BioNTech be shipped to African countries. These would be staffed with staff from that company, which also proposed a new regulatory process whereby the EMA (European Medicines Agency) certifies the container factories. This proposition was seen as "paternalistic and unworkable" (Davies, 2022))

and in our view rather colonial. The pan-African WHO initiative has a vision to ramp up production of vaccines from a currently meagre 1% up to 60% by 2040, using the centre of excellence approach.

Planned and New Vaccine Plants Triggered by Covid19 Vaccine Nationalism

Covid-19 accelerated urgency for local manufacture of vaccines. Ghana, Morocco, Senegal, South Africa, Uganda and Kenya amongst others announced plans to establish new manufacturing plants (Table 10.4). South Africa broke ground for a new vaccine manufacturing plant for NantSA raising the number of local vaccine manufactures to three. Previously, government responses to support the sector had been rather lethargic. The African Vaccine Manufacturing Initiative (AVMI), an industry association had been lobbying governments for years without much progress. Covid19 vaccine intervention failures suddenly focused attention on the urgency of the calls.

The technologies under consideration include mRNA vaccines and therapies for HIV, TB, oncology and other coronaviruses (Table 10.4). These are huge projects with some forecast to cost USD 500 million, and actors involved include the private and public sectors and public–private partnerships.

These new developments are welcome. However, public policy decision-making during crises can obfuscate issues. Developing sustainable value chains, optimising production processes and securing the technological capabilities take time and effort, and require social capital to build relationships of trust. Creating markets for the vaccines was ignored in all the flurry to establish local plants. Table 10.4 shows some of the announced new investments, and sources of funds are from USA and Europe as well as governments. This produces tension from two perspectives: the threat of dependency and the risk of hegemonic behaviour given the drive for profit maximisation and repatriation.

However, another way to consider this strategy towards biologics would be to focus on capitalising on every opportunity for technology transfer, technological learning and structural change of the industry. The technology transfers in biologics are not only from USA and Europe. Countries in North Africa for example have engaged in technology transfer from Russia, Israel and China. Outside the biologics sub-sector, an executive for an East African pharmaceutical firm described dynamics

Table 10.4 Expressed interests in new investments in Covid19 vaccine manufacturing on the continent in 2022

Country	*Investor/collaborators*	*Investment*	*Products/technology*
Potential candidates- South Africa, Rwanda or Senegal	[9]Moderna	USD 500 million	mRNA vaccines API manufacturing, bottling and packaging capabilities
South Africa, Cape Town	Transfer technology NantWorks in USA. NantWorks SA works in collaboration with CSIR (Council for Scientific and Industrial Research Council), SA MRC (Medical Research Council) and SA universities	ZAR 3 billion	Covid Vaccines and vaccines targeting cancer, TB and HIV
Senegal	Team Europe, EU, European Investment Bank, France and Germany. Institut Pasteur de Dakar will host the regional manufacturing hub	Team Europe—Euro 6.75 million. BMZ supporting the manufacturing hub with Euro 20 million[10]	Vaccines
Ghana	Recent talks with BioNTech	Government of Ghana seed funding of USD 25 million	Vaccines

(continued)

Table 10.4 (continued)

Country	*Investor/collaborators*	*Investment*	*Products/technology*
Morocco	Senyso Pharmatech in partnership with Swedish company Recipharm	Euro 400–500 million required	API for more than 20 vaccines; 3 against coronavirus with anticipated coverage of 70% of Morocco's needs and 60% of Africa's needs[11]
Kenya	Already set up Kenya Biovax Institute Limited. Initial plans were to set up a PPP, but Covid19 accelerated local manufacturing plans and the government has funded everything to date	Sh 2.5 billlion	Covid and other vaccines

Source Compiled by authors from various sources,[12,13]

where expatriates from India transferred technology and left when locals were running the plant. So significant were the efficiencies in that local plant that the parent company in India would send staff to learn from it.

However, the source of funds being foreign is concerning. It seems there is still need for a radical change in the science paradigm on the continent. Long-term patient funding for these kind of technological projects needs to come from local sources. The risk that projects fail and the need to create markets for the new products is an area that governments can shape. Innovative procurement can be used as active industry policy to signal to the industrialists and private financiers that a product will have a market (Chataway et al., 2016) thereby creating risk appetite for funders.

Biologics as an Incremental Innovation on Vaccines and Molecular Biology Techniques

Although the biologics manufacturing footprint on the continent is small, it can be expanded. This will entail government investment in infrastructure, policy and institutional support to encourage technological learning.

Afrigen Biologics demonstrated that skills for reverse engineering and technology transfer exist on the continent. Biologics manufacturing is not a new phenomenon for research institutions and biologics manufacturers. With the right investments, science, industry and health policies, technology transfer is possible. However, there is a need to change pervasive colonial science systems in many countries which focused on establishment of local health and agricultural research centres (Clarke, 2013, 2018), for settlement and supporting trade with empire (Hodge, 2011; Worboys & Petitjean, 1996). Therefore, science systems and economic development imperatives need to be decolonised in order to establish institutions and infrastructures for high-tech value chains. National governments need to invest in creating innovation ecosystems for biologicals manufacture, including revision of the university curriculum to support appropriate education and training of professionals for industrial innovation.

Biologics technology complexity compared to chemical synthesis production methods for small molecules (drugs) makes it harder to adapt for current drug manufacturers. The sector deals with living entities and requires different skills sets, types of technology, production processes, approaches to quality assurance and distribution logistics. Hence, whilst biologics are a disruptive innovation for drug manufacturers, they are an incremental innovation for biologics (vaccine) manufacturers. Expanding biologics manufacture to RNA therapeutics would be easier for African universities, vaccine manufacturers, specialist research institutions such as KEMRI in Nairobi Kenya and biologics companies in for example South Africa. These organisations possess the requisite skills in cell and molecular biology, biotechnology, microbiology, virology and immunology. Transition to more complex technologies will require active learning and knowledge upgrading. Technological knowledge tends to be localised, embodied in people and technology and is embedded in routines and linkages between organisations. Thus, knowledge upgrading requires an interactionist approach (Lundvall, 2007, p. 107).

Table 10.5 shows the increasing complexity of technological capabilities with transition from whole cell to nucleic acid-based vaccines. However, most of the typical production processes are based on fermentation and cell culture techniques. Nucleic acid therapies leverage genome sequencing capabilities to chemically synthesise cDNA (Copy DNA) which can be inserted into commercially available or in-house developed vectors. These are used in fermentation or other processes to produce

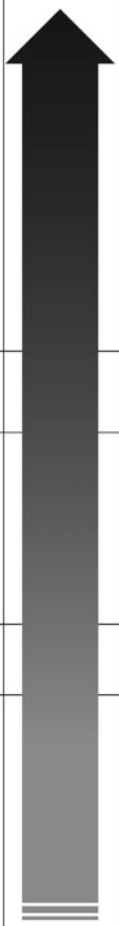
the required antigens. Genomic sequencing, cDNA synthesis and insertion of the required gene into a vector are commonplace activities in research and innovation communities in universities, research institutions and public and private research institutions. On-boarding these activities for biologics production should not be an onerous task given the incremental innovation nature and the opportunities to learn routines and linkages amongst different actors in the ecosystem using the interactionist approach (Lundvall, 2007).

The incremental/disruptive innovation concepts also apply to regulatory processes. One of the challenges faced by regenerative medicine arose when regulators tried to panel-beat the drugs regulatory system to fit that of living entities (Mittra et al., 2015). They argue that life science processes are a disruptive innovation for chemical synthesis regulatory processes. Regenerative medicine, they argued, may have been better served by the blood and blood product regulatory systems, since the processes display greater similarity. So for the regulators, shifting from regulating blood and blood products would be an incremental innovation.

In conversations with vaccine manufacturers on the African continent, the manufacturers reported regulatory approval challenges. According to industrial interviewees, inspections of premises for cGMP compliance were not a major hurdle. Challenges arose on quality assurance processes. The interviewees highlighted the fact that the "process is the product", unlike in chemical drug synthesis where you can characterise aspects such as chemical purity of raw materials and can subject the end-products to analytical tests. Biologics quality assurance depends on carefully following the production process to ensure that products are similar. Another challenge is that living organisms have inherent variability. The quality assurance process needs to consider this. We found the same phenomenon with regenerative medicine in the UK. This is one of the first challenges regulators experienced with chemical drugs will face when transitioning to biologics regulation.

In previous work on regenerative medicine (Banda et al., 2018) we discussed the "fellow traveller concept". Regulators in the UK admitted that they had to learn from the innovators on the specific idiosyncrasies of regenerative medicine, just as the innovators also learnt about the regulatory systems from the regulators. The fellow traveller concept is aligned with Lundvall's (1992) learning-by-doing and learning-by-searching concepts, and what is fascinating in this instance is the active

Table 10.5 The incremental innovation nature of vaccines types, antigen, production process and skills for incumbent players

Vaccine Type	*Technological complexity*	*Antigen*	*Typical Production Process*	*Skills Required*
Nucleic Acid Vaccines		Plasmid DNA (pDNA)	Fermentation	Microbiology and process engineering
		Messenger RNA (mRNA)	Chemical synthesis	Biotechnology techniques of sequencing, copy DNA (cDNA) production and introduction into a vector
		Recombinant vector vaccines	Cell culture	Cell and molecular biology and process engineering
Recombinant Vaccines		Recombinant protein Recombinant virus	Cell culture	Cell and molecular biology and process engineering
Sub-unit Vaccines		Recombinant protein	Cell culture (mammalian/insect)	Cell and molecular biology
		Polysaccharides and Peptides conjugates	Fermentation -(bacterial/yeast)	Microbiology and process engineering
Bacterial toxoids		Toxoid proteins	Fermentation	Microbiology and process engineering
Whole Cell Vaccines		Live Attenuated Virus	Mammalian cell culture	Cell and molecular biology Biotechnology techniques
		Live attenuated bacteria	Microbial cell culture	
		Inactivated virus	Egg-based or mammalian cell culture	Cell biology or biology
		Inactivated bacteria	Microbial cell culture	Microbiology

Source Adapted by authors from https://www.pall.co.uk/uk/en/biotech/vaccine-production.html, and Blakney et al., (2021)

learning processes between regulators and innovators, a relationship that sometimes can be adversarial.

As the African continent gears up to on-board biologics it may be beneficial that the fellow traveller concept is adopted by industrialists/innovators and regulators, but at the same time still leaving the distance required for objective governance. This is critical as regulating the biologics industry will bring both elements of radical and incremental innovation for the regulators depending on the field they are coming from. If the regulator is coming from the biologics industry, then the science and logic of the production process will be an incremental innovation. However if the regulator has experience with drugs and they are transitioning to biologics then this becomes a disruptive innovation for them. Signs coming from regulatory circles are encouraging, however. For example, the Zimbabwean regulator MCAZ (Medicines Control Authority of Zimbabwe) in February 2022 ran coaching clinics on regulating biologics.

The second challenge that regulators need to watch out for is regulatory ratcheting which leads to gold plating of standards. This phenomenon is usually driven by companies that are first on the market that engage in needless gold plating of standards as a competition tool to make it difficult for technology followers to get regulatory approval (Banda et al., 2018, Tait & Banda, 2016). We have previously argued that in instances where a new-to-the-world technology or innovation is being regulated, then it is important that the principles of proportionality and adaptive governance be applied.[14]

No single country possesses the critical mass of biologics regulatory skills. It will take time to develop these skills and in the early days it is likely that the revolving door notion of poaching skills between regulatory and industry as well as between companies may be common. Thus, it is imperative that skills retention be carefully looked at, and in addition, in the early days, that regulatory collaborations and coalitions such as ZAZIBONA be leveraged to efficiently regulate new plants. ZAZIBONA is an innovative organisational arrangement where experienced and emerging regulators are matched for training. The programme involves Zambia, Zimbabwe, Botswana and Namibia (ZAZIBONA), but lately membership has expanded.

The Market Challenges to Successful Technology Transfer

We have up to now discussed the feasibility of technology transfer and argued that because it is an incremental innovation for vaccine manufacturers, it is possible for biologics to be manufactured locally. We have also discussed how the regulatory systems can be shaped. However, one issue that remains unresolved is market formation for biologics and vaccines. In as much as governments and development organisations have all exhibited tremendous urgency and allocated resources to the establishment of new plants and expansion of existing ones, there has been no clear policy direction on, first, who will buy the products locally and where the resources will come from, and second, which international markets to target to ensure business sustainability.

We have previously argued that enhanced procurement of locally made drugs by public health systems can be used as active industrial policy to shape industrial development (Mackintosh et al., 2016). The challenge of low local procurement is not peculiar to the drug sector. Vaccine manufacturers over the last five or more years have pointed out that local procurement of vaccines is a huge challenge. Many African countries depend on GAVI (Global Alliance for Vaccines and Immunisations) for funding for procurement of essential vaccines. As of 2020, there were at least 33 out of 55 African countries that depended on GAVI for vaccines. GAVI selects countries based on GNI per capita. Countries that fall at or below the GNI per capita of USD1580 over the previous three years qualify for GAVI support. If African countries cannot procure the local vaccines and biologics then procurement cannot be used as a market-shaping tool. However as countries move up into middle-income status, as Kenya is doing, they acquire more responsibility for their own vaccine procurement and scope for innovative local procurement.

Market formation underpinned by strategic local procurement is likely in our opinion to be the Achilles hill for technology transfer and localisation at least for vaccines. The other biologics may have a different trajectory, but this will depend on the vibrancy of both public and private health insurance schemes in the countries. If biosimilars for example lead to better health outcomes at a more affordable cost, then it is possible for patients groups to call for their inclusion on oncology therapy regimes.

We are cognisant of the fact that biopharmaceutical manufacture is not only a technological project. It is also political and feeds into geopolitics debates. It is also a commercial project that generates hegemonic behaviour by commercial incumbents, which is not a new phenomenon. It occurred when Asian countries for example Bangladeshi, Sri Lanka and India began the journey to local manufacturing of drugs (Lall & Bibile, 1978; Reich, 1994) (Chapter 2). The heated issues are driven at macro level by national competitiveness and at micro level by immense commercial competition. Davies (2022) highlights the competition aspects by reporting that Pfizer and BioNTech have argued that sharing technology would not lead to high vaccine manufacturing at the moment because there would be stiff competition for raw materials from current mRNA vaccine manufacturers. These are clearly commercial self-interests at play. In the next section, we explore how Cipla acquired biologicals manufacturing capabilities through acquisition of biologicals firms—a possible avenue for rapid technology transfer for cash rich firms. We further discuss what went wrong with their biologics technology transfer efforts in South Africa- and the lessons for policy.

Technology Transfer can be Difficult—The Cipla Biologics Case Study

Cipla was established in 1935 by Dr. A. K. Hamied with the aim of making India self-sufficient in healthcare needs. It emerged as a technology leader in Indian pharma in the 1970s because of its ability to reverse engineer many internationally patented molecules and successfully launch low priced generic versions in the Indian domestic market. Over the last five decades, Cipla developed extensive capabilities in process R&D and emerged as a supplier of cheap generic drugs around the world. Cipla's international generics strategy received a big boost in 2001 with the launch of antiretroviral drugs (ARVs) in emerging country markets at extremely low prices. By 2012 Cipla was credited with transforming the global HIV-AIDS treatment landscape and emerged as one of the most successful Indian firms with an average annual growth rate of more than 20%.

Over the years, Cipla focused on emerging as a main supplier of APIs (Active Pharmaceutical Ingredients) to other MNCs and selling cheap generic version of drugs. However, the transformation of the Indian

domestic market due to the strengthening of the Indian patent act in 2005 and increased competition from global generic manufacturers, created new challenges for Cipla's business model. In 2000, these challenges forced Cipla to embrace biosimilars as a key area of future growth. However, Cipla faced major hurdles in R&D and manufacturing capabilities. Reflecting the argument that this is disruptive innovation, Cipla had no previous experience of biotech R&D or innovative drug discovery R&D and lacked a manufacturing presence outside of India.

To accelerate biosimilar development in 2004 Cipla created Avesta Biologicals Ltd, a new biotech company in partnership with Avesthagen, an Indian biotech company. Avesthagen was responsible for biosimilar R&D whilst Cipla's role was to scale-up manufacturing and manage sales and distribution in domestic and international markets. In 2007, Avesta Biological acquired Siegfried Biologicals, a biotech company based in Germany, to access biological R&D expertise. Siegfried was a contract-manufacturing company with extensive experience in the development of biologicals including cell line generation, upstream process development and scale-up of manufacturing processes that comply with cGMP. However, in 2009 Cipla decided to dissolve Avesta Biologicals and Therapeutics due to lack of progress on the development of biosimilars.

To overcome this failure, in 2010 Cipla acquired a 25% stake in MabPharm, an India-based biotech firm. In 2011, Cipla helped MabPharma set up a state-of-the-art biotechnology manufacturing facility in India and, in 2014, Cipla gained full ownership of the manufacturing plant by acquiring the remaining 75% share. In parallel to the MabPharm acquisition, Cipla invested $65 million to acquire a 40% stake in Bio Mabs, a Shanghai-based biotech firm aimed at developing ten MAb drugs and fusion proteins against rheumatoid arthritis, cancers and asthma for marketing in India and China.

To complement these acquisitions, Cipla decided to build a biosimilar product portfolio through in-licensing. In 2013, Cipla launched its first biosimilar product, Etanercept, through in-licensing from China-based Shanghai CP Guojian Pharmaceutical Co, remarkably at a 30% reduced price compared to any other competitor brands. In 2014, Cipla in-licensed a second biosimilar, "Darbepoetin alfa", by entering a co-marketing deal with Hetero Drugs, an Indian biotech company. On completion of this deal Dr Jaideep Gogtay, Chief Medical Officer, Cipla explained,

> We look forward to partner with companies in India and around the world to bring wider access of biosimilar products to patients in need. We have been recognised as the partner of choice because of our expertise in specialist therapies and efficient supply and distribution. Therefore, we anticipate more number of deals across therapy areas in the near future. (Express Pharma, 2013)

In 2018, Roche and Cipla entered into an agreement for the promotion and distribution of Tocilizumab (Actemra) and other products. In 2020, it was further expanded to include Roche's highly successful trademark oncology drugs Trastuzumab (Herclon), Bevacizumab (Avastin) and Rituximab (Ristova) to address the unmet needs of cancer patients in India. Cipla used acquisition of firms with specific biologicals skills it did not have as well as entering distribution agreements with external firms.

Cipla in South Africa: A Lesson for Policy

Over the years, Cipla created partnerships in manufacturing, sales and marketing with firms all over the world. In 2012, a new management team initiated a strategy to convert these partnerships into subsidiaries and joint ventures to bolster complimentary capabilities. In 2013, Cipla acquired its distribution partner in South Africa, Cipla Medpro South Africa, for US$512 million and followed that by increasing its stake in a Uganda-based joint venture, Quality Chemical Industries Ltd (QCIL) from 14.5% to 51.05% for $15 million (Economic times, 2013; The Hindu Business Line, 2017). By 2021, Cipla emerged as the third largest market player in South Africa, with 7% market share of the South African private market.

Based on this progress, in 2016, Cipla announced plans to build a manufacturing facility in Durban, South Africa to produce biosimilar drugs, and invested $88m in the facility through its biotechnology subsidiary, Cipla BioTech. However, declines in profit and a 42% drop in earnings before interest, taxes, depreciation and amortization (EBIDTA) led to major restructuring aimed at cutting costs and improving profitability. In 2018, Cipla embarked on an in-licensing strategy to develop a biosimilar portfolio of products for distribution in India and other countries. This change in direction resulted in halting of biosimilar production

plans in India and South Africa. Umang Vohra, Managing Director and Global Chief Executive Officer of Cipla commented that,

> We realised that manufacturing (of biotech drugs) is not important. There are enough efficiencies in the biotech system outside of our own. (Pilla, 2018)

This is a clear lesson for policy. Depending on commercial initiatives is problematic because of the profit motive. When huge projects are launched, they may run at a loss for a number of years before turning over a profit. Such projects, therefore, need patient investors. Commercial interests as is illustrated in the Cipla case, can easily cut off projects that are not immediately contributing to the bottom line or do not, for example, fit the strategy of new leaders.

Cipla dropped the local manufacturing project and emerged as the first company to launch Filgrastim Teva for oncology and haematology patients in South Africa in 2018. Post 2018, Cipla used the partnerships and strategic collaboration route to expand its biosimilar product portfolio and oncology products in Africa and other international markets. For example, in 2020, Cipla entered an exclusive partnership with Alvotech headquartered in Iceland, a leading biotechnology firm for the commercialisation of five biosimilar candidates in the immunology and oncology space. Alvotech will oversee the development and supply of the products and Cipla will be responsible for commercialization and regulatory registration (Alvotech, 2020). Building on that, Cipla set up a strategic collaboration with Alvogen in USA for four oncology products in 2021. Cipla followed up these collaborations with partnership agreements with the global biotechnology company mAbxience in March 2022 with an aim to provide essential oncology and respiratory-related biosimilars in South Africa (mABxience, 2022).

In the biosimilar market, Cipla is creating a product portfolio through in-licensing and investing in expanding its international presence by converting its existing partnerships into company-owned subsidiaries. This indicates that the company is using its cash rich status, strong complementary capabilities in sales and distribution infrastructure and leveraging partnerships and acquisitions for creating a biosimilar portfolio.

Conclusion

We have argued that it is feasible to engage in technology transfer for manufacturing of biologics on the African continent. The basis was that biologics are an incremental innovation for the vaccine manufacturing sector in terms of the platform technologies, production processes, quality assurance and regulatory systems. The skills in cell and molecular biology, microbiology, biotechnology and fermentation technology already exist in African universities, specialist research institutions and the private sector. Thus, the foundational base for technology, slim though it might be, actually exists on the continent. This base can be supported with concerted efforts that carefully nurture biologicals innovation ecosystems. Cipla used a faster approach through acquisitions; however, it changed its mind to in-licensing. The acquisition approach requires access to a huge chest of funds. Given the financial limitations of most existing generics firms in African countries, this approach may not be available to many except for companies such as Aspen. The Cipla South Africa local manufacturing failure is an important lesson for policy. Dependence on external commercial interests and funding for technology transfer in high-value manufacturing sectors can be problematic if strategy at the parent company changes and leads to divesture from particular technologies or ventures.

The fellow traveller concept is one of the approaches that can be used to develop regulatory capabilities and scale, and in addition whilst applying the principles of proportionality and adaptation. Solving the politico-technological aspects of the projects is only part of the journey. Markets, market formation and demand structuring are important. Until the procurement of drugs, biologicals and especially vaccine is resolved and based on local resources, sustainability may be compromised. However, we still argue that biologicals manufacture on the continent is feasible and this can significantly improve cancer care and pandemic preparedness.

Notes

1. https://www.who.int/news/item/18-02-2022-who-announces-first-technology-recipients-of-mrna-vaccine-hub-with-strong-support-from-african-and-european-partners.
2. https://www.unaids.org/en/resources/presscentre/featurestories/2021/october/20211021_dose-of-reality.

3. http://www.oecd.org/site/innovationstrategy/defininginnovation.htm.
4. https://www.egypttoday.com/Article/1/113073/Egypt-produces-over-30M-doses-of-Sinovac-VACSERA-COVID-19.
5. https://twitter.com/i/broadcasts/1OwxWzqXnlRJQ.
6. https://ec.europa.eu/commission/presscorner/detail/en/ip_21_3562.
7. https://www.pasteur.sn/fr.
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9. https://www.reuters.com/world/africa/moderna-plans-mrna-vaccine-factory-africa-2021-10-07/.
10. https://ec.europa.eu/commission/presscorner/detail/en/IP_21_3562.
11. https://www.france24.com/en/live-news/20220127-morocco-starts-construction-of-anti-covid-vaccine-plant.
12. https://twitter.com/i/broadcasts/1OwxWzqXnlRJQ.
13. https://ec.europa.eu/commission/presscorner/detail/en/ip_21_3562.
14. For a more detailed description of proportionate and adaptive governance of innovative technologies, please see Tait and Banda (2016).