**Molecular Pharming for Low and Middle Income Countries**

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**Abstract**

Interest in applications and benefits that Molecular Pharming might offer to Low and Middle Income Countries has always been a potent driver for the research discipline, and a major reason why many scientists entered the field. Although enthusiasm remains high, the reality is that such game-changing innovation would always take longer than traditional uptake of new technology in developed countries, and be complicated by external factors beyond technical feasibility. Excitingly, signs of increasing interest by LMICS in Molecular Pharming are now emerging. Here, three case studies from Thailand, South Africa and Brazil are used to identify some of the key issues when a new investment into Molecular Pharming manufacturing capacity is under consideration. At present, academic research is not necessarily addressing these issues. Only by understanding the concerns, can members of the academic community contribute to helping the development of Molecular Pharming for LMICs by focusing their research efforts appropriately.

Starting in the 1980s, when the concept of Molecular Pharming was born, the potential benefits to health in Low and Middle Income Countries (LMIC) have been a major driver for academic research, public funding and general interest in the field [1]. But apart from academic programmes focused on global and emerging infectious diseases, there has been little tangible evidence for those benefits becoming reality. However recently, the first signs of emerging interest seem to have become established.

The use of ZMapp under emergency use authorization during the 2014-2016 Ebola virus outbreak in West Africa was an important breakthrough for plant made pharmaceuticals [2]. For a disease which had been largely ignored because, in the words of the Director-General of WHO, Margaret Chan “ …Ebola has historically been confined to poor African nations… . A profit driven industry does not invest in products for markets that cannot pay”, ZMapp was one of the only active options available to treat patients infected with the virus [3].

Historically, manufacturing pharmaceuticals in developed countries with established pharmaceutical facilities, and provision or donation to less developed countries has been the main approach to addressing Global Health needs [4]. As indicated by Margaret Chan, without incentive, the large pharma industry is unlikely to invest in the necessary research and development for developing country products that are not perceived as high priority [5]. An alternative approach is to develop a manufacturing platform that could be accessible and affordable for LMICs, and Molecular Pharming could offer potential solutions in this respect [6].

Molecular Pharming is still a nascent biotechnology, but the building of manufacturing capacity around the world is an indication of significant growing interest. Whilst the first generation of molecular pharming facilities was established in the global North (USA, Europe, Israel, Japan), where there is experience in early investment into developing technologies, plans are now emerging for setting up Molecular Pharming manufacturing capacity in less expected regions. The most advanced planning comes from Bio-Manguinhos in Brazil for a facility in Fortaleza, announced in 2016 (https://www.ceara.gov.br/2018/11/30/inovacao-em-medicamentos-a-partir-de-plataforma-vegetal-e-pauta-de-encontro-promovido-por-bio-manguinhos-fiocruz/).

Thus, it is timely to consider the decision making process that might result in a relatively large investment by a low and/or middle income country (LMIC), into a new technology to address local health needs. In this review, we will present perspectives from three countries in three continents – Brazil, South Africa and Thailand, from scientists who are or who have been engaged in local considerations for developing commercial Plant Molecular Pharming. We focus on the following key areas:

1. Why a country with limited infrastructure in pharmaceutical manufacturing might choose to invest in plant Molecular Pharming, rather than manufacturing capacity in conventional fermentation systems, which are potentially less risky.

2. What considerations are most important in choosing and prioritising lead products?

3. How could funding for an infrastructural investment be secured? What partnerships, if any are needed?

4. In an LMIC, how would sufficient specialist expertise be developed and a local workforce trained to work in new manufacturing facilities?

5. How might regulatory engagement and approval be developed effectively in a LMIC?

The three countries were selected because they have all considered or are considering introducing Molecular Pharming manufacturing infrastructure, involving high level discussions that have extended beyond researchers, academia and early stage product development. Coming from different continents, each of these countries have different health challenges and priorities, but all are faced with the same issues of growing populations and increasing cost of health provision. Through their case studies, we will seek to identify potentially common influencing factors, hurdles and gaps. Finally, by reviewing the Molecular Pharming literature over the last 12 months, we will assess whether the scientific community is contributing appropriately to the realisation of Molecular Pharming in LMICs.

Thailand

Biopharmaceutical products have been a focus of the Royal Thai government since 2004 with the implementation of Thailand’s National Biotechnology Framework. Biopharmaceuticals is one of ten industries identified as new economic growth engines in the recent “Thailand 4.0” growth model. However, the success of biopharmaceutical commercialization in Thailand remains challenging with only a few biotech companies successfully launched, including Bionet Asia, a vaccine-focused company; Siambioscience, establishing the first mammalian cell-based platform; and the government pharmaceutical organization (GPO) developing influenza vaccine using egg-based technology [7]. Opportunities for technology transfer from developed countries have been limited, although a public-private partnership was established in 2013 between the GPO and Sanofi (GMP-MBP) to develop a new combination vaccine for diphtheria, tetanus, acellular pertussis and hepatitis B.

Molecular Pharming research in Thailand is still in its infancy and transgenic plants are banned in Thailand. The first Molecular Pharming papers from Thai scientists were in 2017 [8]. Interest in investment in Molecular Pharming platforms only resulted from push by academic researchers hoping that plants could be an alternative platform for local biotechnology industry development.

Self-reliance, national security and increasing access to medicine have been major drivers for expanding investment in biotechnology platforms. The advantages of Molecular Pharming such as scalability, speed, versatility, low production cost, and local raw materials has drawn the attention of policy makers in Thailand. The latter point is important. Instead of importing chemicals and media at higher cost compared to US or Europe, a technology that uses locally available raw materials has potential economic advantage.

However, there is hesitancy around the risks associated with an emerging manufacturing platform, versus more established platforms which have benefited from more investment, and are already generating many approved products. Policy makers are reluctant to invest in a technology that does not have many products on the market. There is also recognition that it is difficult for the national regulatory body, the Thai FDA, to approve a drug from novel technology that has not been previously approved by other countries with better established biopharmaceutical manufacturing and regulatory systems. This is a major hurdle for government and private investors. The Thai FDA follows guidelines from US FDA or the European Medicines Agency, so prior approval elsewhere greatly accelerates approval in Thailand.

Thailand has an established national vaccine strategic plan and many biologics relevant to that plan have been reported as being produced successfully in plants. These vaccines include Dengue [9,10], Japanese Encephalitis [11], tuberculosis [12] and influenza [13]. In this regard, the Molecular Pharming community can be seen to be supporting the needs of a developing manufacturing system in countries like Thailand. In addition, expensive biological products, such as immunotherapy drugs, are also attractive to policy makers and private investors, as targets for low cost manufacturing through Molecular Pharming which could by-pass the need for expensive licensing agreements. The Thai GPO has a mission to research and develop new pharmaceutical products and medical supplies to respond to the needs of Thai society. The GPO has registered an interest in Molecular Pharming because of its potential use for epidemic diseases and preparedness for emerging diseases. Another GPO mission is to develop business in order to ensure competitiveness and self-sustainability, so the GPO is also looking for high-value products such as cancer antibodies, from molecular pharming to generate revenue.

Although Thailand still lacks the human resource to support development of any biopharmaceutical platform, several grant agencies support training expertise for the vaccines and biopharmaceuticals industry. Some of this training will be generic across multiple platforms, such as expertise in Quality Control and Quality Assurance. The immediate solution is to recruit capable scientists from overseas, or work collaboratively with international partners, an example being the GMP-MBP partnership. Universities need to be part of the longer term solution, encouraged to set up programmes to train people in key strategic fields, such as plant biotechnology and downstream processing.

South Africa

In contrast to Thailand, South Africa has a longer than 20 year history of research in Molecular Pharming, and major government-linked funders have consistently supported research in this area [14]. For example, the Technology Innovation Agency (TIA) and the government Department of Science and Technology (DST) have both made substantial grants to the two major groups involved in this field, as it represents the kind of novel biotechnology that is of interest to South Africa’s National Bio-Economy Strategy (https://www.dst.gov.za/index.php/media-room/communiques/801-media-release-launch-of-south-africas-bio-economy-strategy).

Part of this Strategy is to secure a supply of prophylactics and therapeutics, whilst developing the ability to manufacture pharmaceuticals, vaccines, diagnostics and medical devices to address disease burdens. The three priority areas that were identified for research and development are agriculture, health and industry/the environment. One focus area is the development of vaccines and diagnostics kits for diseases that pose a huge burden to South Africa [15,16], including TB and HIV, whilst also targeting devastating outbreaks of livestock diseases such as foot and mouth disease [17] and African horse sickness [18] in the agricultural sector. Development of biosimilars is envisaged to reduce the costs of importing pharmaceuticals [19,20], however product selection and development is often driven by research at universities with funding by scientific councils.

The main hurdle to establishing a plant-made pharmaceutical (PMP) production facility is the scale of investment that is needed. As it stands, to build a reasonably-sized biopharming facility will cost around USD 20 million, which is beyond the scope of most government funding bodies. In addition, the staffing and continued running of such a facility requires long term investment by the government or other funders, which is also a major hurdle.

Recently, the South African government, via its Department of Trade and Industry (DTi), co-invested in Cape Bio Pharms, a small-scale biopharming facility in Cape Town, in an approach that could be used as a model for government investment into new technology. A Technology and Human Resources for Industry Programme (THRiP) grant was awarded, aiming to boost South African industry by supporting research and technology development. The three year funding is in the form of a 50:50 cost-sharing grant with the company, and one of the key objectives of this scheme is to increase the number of people with skills in development and management of research-based technology for industry. The company is required to partner with a university or higher education institute where students are enrolled in postgraduate studies in their specific field of interest, and these students are then funded by the scheme. It is envisaged that the students will, on graduating, be employed by the company or by similar industries. Funding of Cape Bio Pharms as a start-up biopharming company is a good model for setting up a small PMP manufacturing facility in South Africa, but expensive equipment for downstream purification is not included in the grant and will have to be funded from other sources. Thus, routine manufacture of PMPs in South Africa will still take a few more years.

Regulation and approval of pharmaceuticals is well established in South Africa, although the regulatory bodies are generally restricted by understaffing and limited expertise in novel areas. However, Protalix Bioteherapeutic’s plant-made Elelyso was trialed in the country, so South African regulators have some experience with Molecular Pharming products. New products are not usually approved on the basis that they have been approved elsewhere, and the normal requirement is that they need to go through the South African process of approval. For this reason, engagement with regulatory bodies right from the onset of product development is strongly advised to speed up approval of products.

Brazil

Of the three countries profiled here, Brazil has the most advanced pharmaceutical industry and is actively engaged in establishing a manufacturing facility based on Molecular Pharming. A R $737.6M (~US $180M) investment into the Centro Tecnológico de Plataformas Vegetais (CTPV) was made by the Brazilian Ministry of Health through Bio-Manguinhos, a unit of the Osvaldo Cruz Foundation. Building was started in 2017 and the facility is targeted to open in 2022 (<https://www.bio.fiocruz.br/index.php/home/crescimento-institucional/campus-eusebio-ce>).

Plant-based technologies are very new for Brazil, and it was recognized that there are still challenges to overcome, but the national decision to invest in plant manufacturing platforms was based on a combination of factors. Although other expression systems (Chinese Hamster Ovary Cells – CHO, and *E. coli*) are dominant in the pharmaceutical industry, there has been increasing investment in diverse platforms around the world. One of the reasons for this is that no one platform provides a “fit-for-all” approach. Some drug targets are better expressed in one system, while others are better in other systems [21]. Secondly, there are still important limitations in terms of costs associated with the more mature expression systems. A further consideration was the lack of space for new entrants, particularly from LMICs, in existing pharmaceutical expression platforms. With plant-based platforms, the possibility of developing new intellectual property associated with existing high-value products that are produced elsewhere by technologies such as CHO, might give a Brazilian company more opportunity to enter the market of recombinant vaccines, biotherapeutics and diagnostics, either through new products, biosimilars or biobetters. Moreover, as is the case in Thailand, Brazilian experts recognized that production costs associated with importing raw materials such as culture media, plastics and devices are often a problem alongside the implementation of bacterial or CHO fermentation systems. Plant-based production processes require simpler culture media, which are readily available locally and are less costly. Linked to this, is the low risk posed by potential zoonotic agents in plant growth media, compared with media for mammalian cell culture.

When the decision to invest in plant-based technologies in Brazil was made, Bio-Manguinhos presented a project to Federal Government for capital investment funding. This has since become an area of long-term strategic technology investment. However, government funding was not the only critical success factor. Since plant-based technologies are much more recent in Brazil than in other countries, partnerships were highly important not only with leading companies but also with universities and technology and research institutes. Part of the investment into the CTPV was in association with the Israeli company Protalix Biotherapeutics, with an agreement to establish their plant cell culture platform in Brazil to produce alfa-taliglucerase, their commercial Molecular Pharming product. To encourage other partnerships, two international research meetings were organized in Fortaleza, close to the site of the new facility, involving academia and many organizations working in the field. Partnerships are being sought at different stages of product development, as well as for platform implementation and capability building. It is helpful that Brazil is an important market for biological health products, making it an attractive partner for pre-clinical and clinical co-developments.

There has also been investment into initiatives to support target identification and prioritization. The prioritization of lead products in Brazil is largely determined by the requirement to meet Brazilian public health needs regarding improvement of access to medicines, with high quality standards, lower costs for Government’s pharmaceutical assistance programs and reducing technological dependency, so as to reduce the technology trade balance deficit. This of course, reflects the nature of the national investment, rather than a decision based primarily on commercial grounds. In addition to the alfa-taliglucerase partnership with Protalix, a vaccine for yellow fever, a significant problem in Brazil [22] , was also identified as a priority product for development in plants.

The development of relevant specialist expertise will rely not only on internal investments in higher education, technical education and research projects, but also on partnerships with leading groups and companies towards training in pilot and manufacturing facilities, and laboratory research. For the investment to materialize and leverage local product and process development capabilities, building new infrastructure was necessary. For this reason, the first capital investment was in a new R&D facility. These research facilities constructed for plant-based platforms are specifically designed to increase capabilities to work in product and process development using different approaches like transgenic and transient expression, as well as plant cell culture.

With its experience in pharmaceutical manufacture across conventional platforms, Brazil is well placed to develop appropriate regulatory oversight for new technologies like Molecular Pharming, even though the first biotechnology regulation in Brazil only came into force in 2002. With little or no previous experience with plant-based technologies, at the first international research meeting in 2013, Brazilian regulatory representatives were invited to start the discussion about this new area. As knowledge on the platforms has grown in Brazil, at the 2018 meeting, the Brazilian Health Regulatory Agency (ANVISA) committed to create a group to discuss a framework that could be applied to plant-based development and manufacturing. ANVISA is also engaging with other organizations such as ICH and PIC/s in order to adopt their guidelines.

**Perspectives and Summary**

As a representation of Molecular Pharming developments in LMICs, these three case studies provide a valuable snapshot into current thinking by countries that are amongst the more likely to lead the way for the field. There are common themes which are also consistent with anecdotal comments from experts within the discipline. For example, establishing biotech-based drug manufacture is often in line with Government strategy and the key drivers are to reduce costs, to improve national access to medicines, and to reduce dependency on external providers. For plant manufacturing, in addition to the potential advantages of cost, scalability and safety that are well known [6], the opportunity to reduce the supply chain complexity and cost for raw materials was highlighted within these discussions. Interestingly, the pressure for commercial sustainability and income generation is an additional driver that has important influence on the selection of target products.

Lack of regulatory expertise and experience is often cited as a key barrier to acceptance of new technologies in LMICs and this has been a running theme for many years [23]. The experience and approach in South Africa and Brazil suggest that this may not be as significant a barrier as originally perceived. To some extent, the introduction of products that are already accepted by other regulatory bodies alleviates the issue, and Protalix’s Elelyso appears to have been a key “ice-breaker” in South Africa and Brazil. Likewise, the establishment of public/private partnerships with large pharma companies, as implemented in all three countries appears to be a successful strategy to mitigate cost and risk.

The role of research academics is cited as being a key influence for adoption of new technologies, and this was reinforced in the South African and Thai case studies. Developing impact from nationally funded research has universal appeal, and takes advantage of locally produced intellectual property. This is perhaps a key area where research academics can play an important role in influencing the “big picture” [24].

Another important role research academics can play is to influence public perceptions of Molecular Pharming. Within the European Union, research funded from the Horizon 2020 programme includes a remit to explore and improve social perception of the innovations being developed within the grant funding scheme. This is part of the Commission’s adherence to the Responsible Research and Innovation (RRI) framework [25], which is premised on multiple stakeholder inclusion and consultation at the earliest stages of scientific and technological development, with the view that new technologies should both respond to and drive societal transformation. RRI and other methods of co-production, such as action-oriented and participatory theories within the social science and humanities share the perspective that research outputs should primarily serve the needs of society-at-large and, as such, include discourse with civil society [25,26]. Societal perceptions also have implications for policy development [27,28]. This will be particularly important should Molecular Pharming, which relies on modified plants, move beyond contained facilities into ‘the field’. In an increasingly global health economy, policies in Europe and the United States have an impact on the rest of the world [29].

The current European policy on genetic modification is likely to limit the scale-up and scale-out of Molecular Pharming [30,31]. Conversely, openness of policy toward Molecular Pharming in LMICs may pose opportunity for scale-up of these technologies and in so doing, create a virtuous circle of open civic dialogue alongside concrete examples of valuable, nationally produced, recombinant vaccines, biotherapeutics and diagnostics. The promise that Molecular Pharming has for improving LMIC’s public health and economic independence provides a great opportunity to improve the perception of the technology both within and beyond LMICs [32].

Are these high–level national aspirations reflected in the scientific literature?

Without doubt, the most important and persuasive arguments for investing in plant-based manufacturing come from regulatory acceptance, approval and licensing of products and commercial success. But, it also seems important for LMICs that a strong list of relevant candidate products is in the development pipeline. In order to assess the current level of “push” from research academics in Molecular Pharming, we reviewed the 48 papers that included “molecular pharming” or 'plant recombinant protein production’ as key words, which were published in a 12 month period in 2018-2019. Of these, over half (n=25) of the publications described research addressing a disease predominantly affecting LMICs. A high proportion of publications (19) were from research groups where the corresponding author was affiliated to a LMIC institution (defined according to the DAC list of ODA recipients by OECD) (ref), and 13 of those 19 publications addressed a LMIC specific disease target.

Most of the papers described the expression of candidate vaccines (18), antibodies (8), anti-microbials (8), enzymes (4) and growth factors (4), so it does appear that researchers are working in the right areas to help technology development. However, it was noticeable that almost all the papers described very early stage work (Technology Readiness Levels 1-3), with only two publications going on to describe formal pre-clinical or clinical development of products (13,18). So the field is still primarily in a similar position to the one that it has been in for over twenty years – predominantly reporting interesting proof of concept findings, with very few candidates being taken further, beyond initial research publication.

This is disappointing given the increasing examples of Molecular Pharming products that have entered clinical trials, which have demonstrated the absence of any serious regulatory hurdles. A clear message to the Molecular Pharming academic community therefore, is that if the objective of establishing molecular pharming in LMICs is to be realized, then more emphasis needs to be placed on working towards second and third research paper outputs focusing on product development for new drug candidates.

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