

The Landscape of Biologics Drug System in Thailand

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Abstract Biologics, breakthrough pharmaceutical products that change the treatment paradigm of many diseases, have unique characteristics that could impact country drug system overall. The aim of this study is to analyse the current situation of biological drugs and gaps in Thailand drug system. We have found that regulations of most biological products in Thailand have been developed slowly and is currently up to international standard and Thailand is currently drafting a new cell therapy act to better regulate advanced therapy medicinal products. While regulations of biologics are not a major concern, access to innovative biologics that are high cost is still an issue. Strengthening research and development of biologics in the country is a key activity done by the Royal Thai Government to lower the cost, improve accessibility and boost Thailand economic growth while innovative pricing mechanisms for high-cost drugs is utilized as a short-term strategy to increase access. The infrastructure of the supply chain of the drug is largely well-established through existing vaccine cold chain system. Human resources development for every sector along the value chain of the biologics drug system is, however, an urgent issue and should be addressed to strengthen the biologics drug system in Thailand.

Keywords: biologics; vaccine; access; research and development; personalized medicine

Introduction

Biological products, also known as biologics, are breakthrough pharmaceutical products that change the treatment paradigm of many diseases. The unique

characteristics of biologics include its composition, size and structure, complexity of product development and manufacturing process, stability of the product and its immunogenicity.⁽¹⁾ Biologics are produced from

living cells (such as bacteria, plant or animal) and therefore the product itself is dependent on the manufacturing process. Any small changes in this process may change the safety and effectiveness of the product. The best-known biological products, such as vaccines and insulin, have been available for a long time. With progress in recombinant and hybridoma technology, biological products now available in the market have become more advanced and include bloods and derivation of bloods, vaccines, monoclonal antibodies (mAbs) and proteins and advanced therapy medicinal products (ATMP). Globally, and in Thailand, biologics have become increasingly more important, yet the overall landscape of how biologics could have an impact on the Thailand drug system is still not clear.

The objective of this study is to review the landscape of biological drug products in Thailand. The scope of this study includes the analysis of the current situation of biological drugs including the regulation, patient access biologics, distribution and selection of biological drugs as well as the review of what have been done to bridge the gap in Thailand biological drug system.

Methods

We employed a mixed-methods study comprising a literature review and an in-depth interview to describe the current landscape of biologics in Thailand. PubMed and Google Scholar were searched for any articles explaining the biologics situation in Thailand. We also searched government official websites for any grey literatures or official documents relating to biologics drug situation. In-depth interviews with selected key

informants including government officials from for example, Ministry of Public health, Department of Disease Control, regulatory agency, experts in biological products, and pharmaceutical companies were conducted to retrieve information not available in the literature, as well as to confirm information retrieved from the literature.

Results

Data from Thai Food and Drug Administration (Thai FDA) has shown that national spending on biologics has increased tremendously from US\$547 million (16,513 million Thai baht) in 2009 to US\$ 1,664 million (50,182 million Thai baht) in 2018. Biological products used in Thailand are mainly from importation (96.0% biologics spending) making Thailand mainly an importer in the overall global biological market.

Regulation of Biological Products in Thailand

Before 2009, many advanced biological products were classified as “new drug” not “biological product” category. Several biologic products such as vaccine, insulin, recombinant human erythropoietin, bevacizumab, rituximab, trastuzumab and filgrastim were market authorized using criteria for chemical drug products approval. In 2009, the ASEAN harmonization of pharmaceutical registration came into effect.⁽²⁾ With the mutual recognition of the ASEAN Common Technical Dossier (ACTD), the Thai FDA announced criteria for new biological product approval. At that time, Thailand also experienced a higher incidence of pure red cell aplasia (PRCA), which was suspected to be a severe adverse drug reaction caused by

epoetin. The Thai FDA and other stakeholders including pharmaceutical industry and clinician collaborated to investigate possible causes of PRCA and also reviewed the safety, efficacy and quality of epoetin product registration. Several epoetin products granted both before and after having biological product approval criteria in 2009 were included. After reviewing, it was found that almost 20.0% of the approved dossiers did not have clinical evidence support and 44.0% of them did not use randomized controlled trial study design. The ad hoc committee provided suggestions to improve the regulatory control system which includes the development of biosimilar submission criteria, a request to the pharmaceutical company to submit a risk management plan with the biological drug application, and the re-submission of the epoetin dossier which needs additional documentation.⁽³⁾ Since then, the Thai FDA have announced several process and criteria relating to biologic product registration as well as criteria to regulate post-approval change such as marketing authorization procedures for vaccines in 2009, updated new drug and new biological product registration criteria in 2015,⁽⁴⁾ updated criteria for biosimilar registration in 2018,⁽⁵⁾ and updated criteria for new drug and new biological product registration in 2018,⁽⁶⁾ and issue criteria specific for regulating post-approval change of vaccine as well as biotherapeutic proteins in 2019. At this point, regulation of the biological products was raised up to international standard.

Regulating biologic products is not only needed at the marketing authorization phase, but also throughout their product life cycle. Since 1999, the Thai FDA employed a safety monitoring programme (SMP) for new drugs including all new chemical, vaccine and

biological drugs.⁽⁷⁾ Under the SMP, new drugs were conditionally approved and were classified as specially controlled medicines. The safety of these new drugs needed to be monitored. The products were distributed restrictively in healthcare facilities under physicians' close supervision. The Thai FDA required the company to facilitate the reporting of their product's adverse drug reaction (ADR) to the Thai FDA in an appropriate timeframe for at least over a two-year period. After two years, the summary of safety data was re-considered. If the safety data is satisfied, the products' condition of restrictive distribution can be removed.

Since many biologics are used to treat life-threatening diseases, market approval decisions can therefore sometimes base on the surrogate endpoint rather than the traditional final and long-term outcome or on the use of incomplete phase 3 clinical trial data. These new drugs have different safety issues and a new risk-based approach SMP, which was introduced in October 2017.⁽⁷⁾ Under the new risk-based approach SMP, new drugs were divided into four categories and the method of safety monitoring was adjusted according to product's risk level. New drugs approved with an incomplete phase 3 clinical trial will be classified as risk level 1. The active vigilance of all patients for at least two years is required. New chemical entities, new derivatives, new indications, new combinations and new biologics will be classified as risk level 2. Intensified spontaneous reporting for at least two years is required. New delivery systems, administration routes, dosage forms and strengths will be classified as risk level 3. Intensified spontaneous reporting for at least one year is required. Other types of new drugs based on Thai FDA criteria are classified as risk level 4. Mandatory spontaneous reporting

according to Thai FDA recommendations is needed.

The Thai FDA has accepted electronic common technical document (eCTD) applications for new chemical entities, new biological drugs and vaccine since 2006.⁽⁸⁾ There were 47, 25 and 37 applications for new biological products and vaccines and 19, 6 and 7 applications for biosimilar products submitted to either the Bureau of Drug Division and Director of Division of Health Product Business Promotion in 2017, 2018 and 2019, respectively. While internal experts (less than 20 staff members) are limited, the trend of biological products is rising. There is a need for more qualified experts to evaluate the biological and biosimilar dossiers, which have a working day time frame of 280 and 230 days, respectively.

More advanced biological products like ATMPs have different regulatory issues. Prior to 2009, stem cell therapy was entirely unregulated in Thailand. As a result, many exaggerated claims and openly advertising stem cell therapies, especially through online channels, were reported. On March 27th, 2009, the Thai FDA announced the control and supervision of drugs and products from stem cells under the Drug Act B.E. 2510. The law required any stem cell use to be first approved by the Thai FDA. However, the law does not include any products created for an individual person and therefore most stem cell treatment used this gap to avoid regulation from the Thai FDA. To control the abuse of fake stem cell treatment, the Thai Medical Council, which governs the practice by licensed physicians, signed the Medical Council's Regulation on Medical Ethics Regarding Stem Cell Research for Human Treatment B.E. 2552 on November 23, 2009. The law became effective on January 11, 2010 requiring all studies on stem cells

to be approved and it controls the use of stem cell treatment in all medical schools, private hospitals and clinics.

With an increasing in the number of advanced ATMPs, the Department of Health Service Support, Ministry of Public Health, Thai FDA, Thai Medical Council and leading academic institutions came together in 2019 to draft a new cell therapy act to better regulate research and development, use and authorization of cell therapy in Thailand. The act will include clear categorization of cell therapy as well as quality standards of cell therapy in Thailand.

Access to biologics through Thailand public health insurance

Patient access to biologics under the Thailand public health insurance system varies between the three main health insurance schemes, which are the civil servant medical benefit scheme (CSMBS), the social security scheme (SSS) and the universal coverage scheme (UCS). National List of Essential Medicine is used as a medicine reimbursement list for patients in all three schemes. From our analysis, there are currently 91 biologics listed in 2019 National List of Essential Medicine (NLEM) (10.3% of 882 drugs listed in NLEM). The most common groups of biologics on the 2019 NLEM are immunological products and vaccines (26 products), whole blood and blood products (23 products) and insulin and drugs for the endocrine system (11 products). Monoclonal antibodies for the treatment of malignant diseases listed in 2019 NLEM included rituximab, trastuzumab and basiliximab, which are listed in the E2 access programme under NLEM. Under the E2 access programme, only specific groups of patients with

specific indications listed in NLEM can be reimbursed. It should be noted that no ATMPs are currently reimbursed under the Thailand public health insurance system. As an addition to E2 access programme, CSMBS beneficiaries have other access programme for the reimbursement of biologics that are not listed in NLEM; for example, the use of prior authorization lists including Oncology Prior Authorization (OCPA), Rheumatology Disease Prior Authorization (RDPA) and Dermatology Disease Prior Authorization (DDPA). CSMBS beneficiaries have access to biologics on the NLEM and OCPA. Biologics have been included in all of these lists. For example, rituximab and trastuzumab were included in the NLEM and also in the OCPA list. However, the indications for both drugs on the OCPA list are broader than on the NLEM. Many biologics are included in CSMBS's negative list; for example, adotrastuzumab emtansine, atezolizumab, denosumab and ipilimumab. This indicates that these medicines would not be reimbursed for CSMBS patients.⁽⁹⁾

The reimbursement of biological products is challenging since the evidence available for the reimbursement of these advanced health biological products is often inadequate when compared to evidence available for conventional treatment. Biologics are also known for their high cost, which is because most of these drugs are still under patent owned by the manufacturer. The price of these biologics can be as high as 20,000,000 Thai Baht per year. Thailand has been using Health Technology Assessment (HTA) as a tool to support decision-making for reimbursement since 2004.⁽¹⁰⁾ Results from economic evaluation and budget impact analysis studies are one of the key criteria used by Thai health policy makers for NLEM

listing. However, with its high costs, payments for biologics mostly fall under Thailand's willingness-to-pay threshold and are not considered to be a cost-effective intervention; for example, the use of Tocilizumab in systemic juvenile idiopathic arthritis is not cost effective. The use of alternative financial models has been proposed to increase patient access to these medicines; for example, the use of managed entry agreement or valued-based pricing or an alternative channel like orphan drugs and rare diseases reimbursement. These alternative financial models become increasingly important for accelerating access to biologics since these drugs mostly treat rare diseases and have high costs and inadequate data required for regular Health Technology Assessment (HTA) process. With an increasing number of biosimilar products, the assessment of these products also becomes an issue. The question is whether to assess biosimilar products as one specific product different to the reference product or to assess it in the same way as chemical drugs where the efficacy of generics is similar to its originator. Currently, there is no specific HTA guidance on biosimilar products but looking to the future, the upcoming National HTA guidelines will have one chapter dedicated specifically for biosimilar products. Since out-of-pocket payments are the main sources of funding biologics, Patient Assistance Programmes (PAPs) become the main financial support for these self-paid patients. PAPs are pharmaceutical company-sponsored programmes that offer brand name medicines by pharmaceutical manufacturer to patients at a lower cost or sometimes at no cost. PAPs currently available in Thailand varied in design and criteria for eligibility for the program. Most programs utilize fixed scheme which

provides the fixed promotional pattern of “Buy X get Y boxes free” for every patient with the same disease condition.⁽¹¹⁾

For vaccines, the access system is slightly different. Access to vaccines in Thailand is provided through Thailand’s Expanded Programme of Immunization (EPI) operating since 1977. The programme provides free vaccines for every Thai citizen as well as immigrants and workers from other countries. Thailand EPI is a centralized program in which the National Health Security Office (NHSO) pay for vaccine and immunization services through its capitation payments to primary care facilities. In 2015, government spending on vaccines and immunization services is US\$58 million and accounted for 0.7% of the total public health budget.⁽¹²⁾ Fifty-seven percent of the spending were on vaccine procurement. In 2019, the Thai EPI programme includes vaccines that cover the following 11 antigens: tuberculosis (BCG vaccine), hepatitis B, diphtheria, tetanus, pertussis, poliomyelitis (OPV and IPV vaccine), measles, mumps, rubella, Japanese encephalitis (JE), influenza vaccine and human Papilloma Virus (HPV vaccine).⁽¹³⁾ The coverage rate of vaccine in the EPI program reach 99.0% of the population.⁽¹⁴⁾ The most recent change in the EPI vaccine schedule is the change from tetravalent vaccines to pentavalent vaccines (DTwP-HB-Hib vaccine). This was mainly due to the addition of the Hib vaccine in the standard vaccine list for Thai children.⁽¹³⁾

Even though access to vaccines in Thailand is not a major issue compared with other biologics, the supply security of vaccines became a concern for the Thai government. Several incidences of vaccine shortage were reported in Thailand; for example, the

shortage of MMR vaccine due to limited supply and high demand in 2013.⁽¹⁵⁾ This raise the issue of supply security of vaccines during both normal situations and pandemic situations, which is a health security concern in the age of globalization and common air travel.

From Manufacturer to Patients

One unique characteristic of biological products is the need for temperature sensitivity. Product efficacy can drop steeply when kept out of the recommended temperature. Therefore, the cold chain becomes an important factor in the biologics supply chain. Along the product life cycle, many responsible stakeholders such as importers, distributors and hospitals are well aware of the special storage condition of biologics. The cold chain system for vaccines has been implemented since 2009 under the Government Pharmaceutical Organization (GPO)’s vendor management inventory (VMI) programme. In the VMI system, the vaccine supply chain starts at the GPO warehouse and goes directly to district warehouses (at provincial and district hospitals). It then goes from the district warehouses to the Primary Care Units (PCUs) including health centres or hospital immunization clinics. The VMI system has been implemented successfully in Thailand.⁽¹⁶⁾ The transition from the conventional vaccine distribution system to the VMI system was viewed positively by staff and implementers. It saved nearly one-fifth of the total cost of vaccine procurement and distribution in its first year of implementation through more efficient use of resources, lower logistics costs and a smaller number of vaccines procured and distributed.⁽¹⁶⁾ The system, however, should improve the quality of vaccine distribution

services between the GPO and the district warehouses. The system should impose quality control measures such as a systematic quality monitoring system and Good Distribution Practice guidelines. Computerized data loggers were placed inside vaccine boxes on each vaccine shipment between some periods of time.

The quality of the product at the district warehouses and health centres is also of concern. Several studies found an issue in the vaccine supply chain. In one study, almost 80.0% of the refrigerators surveyed could not control the temperature within a two to eight-degree Celsius range, which is the temperature range for biologics.⁽¹⁷⁾ Another study found that hospitals used inappropriate power outlets and had no alternative vaccine storage plans for emergency situations. Currently, temperature sensors have been distributed to hospitals and the overall situation could be improved through training, supervision and monitoring.⁽¹⁸⁾

Other biologics such as proteins and ATMPs also require a cold chain for distribution to patients. The break in the cold chain of proteins such as monoclonal antibodies could lead to potential pharmacokinetics and pharmacodynamics alterations to these antibodies as well as to the protein structure, which can lead to harmful immune reactions. For ATMPs and autologous cell therapy (ACT), which is considered as a living drug, Chimeric Antigen Receptor T-cell needs an even more complex cold chain. The production of autologous CAR T cell begins with blood cell collection from the patient, laboratory process of CAR T cells at the manufacturing site, and delivery the cells to site of administration. The whole process requires intensive traceability and tracking system to ensure that the product is delivered to the right patient.

Cellular products are usually shipped and stored as cryogenic freezing to maintain the stability of product. Strict temperature controls and monitoring are recommended throughout this process to ensure high-quality and safe treatment to patients. However, a focus on the cold chain and traceability of these products is still not much discussed in Thailand.

Many biological products were prescribed to patients to administer at home; for example, recombinant human erythropoietin where the patient needs to inject the drug themselves at home. This might present another problem, not yet investigated, as these patients need to store their biological products in household refrigerators. As biological products are highly expensive and easily lose their efficacy when stored in an inappropriate condition, a new drug management system needs to be considered. Patient registration together with the use of a vendor management inventory and refillable biological products at nearby hospitals might be an innovative management solution. On the other hand, research focusing on the development of new formulations to improve temperature-sensitive products is also needed. A study by Kaplan using a self-standing silk protein matrix showed a six-month stability of vaccines and antibiotics in a 60-degree Celsius condition.

What have been done to bridge the gap in the biological drug system in Thailand?

It is obvious that as biologics become more important, access to biologics is a significant issue. In the area of vaccines, Thailand provides access through its EPI programme. One problem with the vaccine system, however, relates to vaccine security issues; for example, vaccine shortages and vaccine availa-

bility in pandemic situations and vaccines for diseases that are region-specific. We have found several initiatives to bridge the gap in Thailand's biological drug system especially to accelerate the growth in research, development and manufacture biologics.

Research and Development of Biologics

In an effort to lower the cost, improve accessibility and boost Thailand economic growth, providing support to the biologics industry has become a focus for the Royal Thai Government. In 2004, the Royal Thai Government implemented Thailand's National Biotechnology Framework. The biopharmaceuticals industry came under the spotlight again in 2013 when it was included in one of ten industries identified as new economic growth engines in the recent Thailand 4.0 growth model.⁽¹⁹⁾ Thailand 4.0 growth model is an economic model that aims to unlock the country from several economic challenges including "a middle-income trap", "an inequality trap", and "an imbalanced trap". Below is a summary of the advances made in the local biological industry, as well as challenges and obstacles faced.

Queen Saovabha Memorial Institute (QSMI): This is the first biologics manufacturing facility in Thailand, established in 1913. It was also the first vaccine manufacturing facility in South East Asia to produce rabies vaccines and immunoglobulin.⁽²⁰⁾ The Institute then became part of the Thai Red Cross society in 1917. Current products manufactured by the Institute include: the BCG vaccine in which QSMI is able to produce from the upstream process; Tuberculin PPD and the Rabies vaccine where QSMI imports bulk products from and performs only downstream manufacturing processes. Other products manufactured by

QSMI include seven kinds of monovalent snake antivenoms, polyvalent snake antivenoms for both neurotoxic and haematotoxic snakes as well as rabies immunoglobulin from equine and human. Also, part of the Thai Red Cross society hosts a plasma fractionation centre which is the only plasma product manufacturing facility in South East Asia. The plasma fractionation centre has transferred the production of plasma-derived products technology from the Korean Green Cross in 2011.⁽²¹⁾ Products from Thai Red Cross's plasma fractionation centre include factor VIII heat-treated freeze-dried cryoprecipitate (HTFDC), human albumin 20.0%, Hepatitis B immunoglobulin for IM, human rabies immunoglobulin for intramuscular injection.

The Government Pharmaceutical Organization (GPO)

Founded in 1964, the GPO is a state enterprise manufacturer of pharmaceutical products under the supervision of the Ministry of Public Health. The GPO started producing vaccines since 1946. It was able to produce mouse-brain-derived inactivated Japanese encephalitis vaccine, diphtheria tetanus and pertussis (DTP) vaccine, snake antivenoms and tetanus antitoxin. These products except Tetanus antitoxin are now all discontinued for several reasons. DTP vaccine was discontinued due to a technical manufacturing issue. Mouse-brain-derived inactivated Japanese encephalitis vaccine was discontinued in 2017 because of the changes to the national immunization policy; there was a switch to the live attenuated Japanese encephalitis vaccines using a cell-based technology platform as it was safer and more effective compared with the mouse-brain-derived vaccine. Snake antivenoms were discontinued since the product line was too similar to

antivenoms produced by QSML.

Currently, the production of vaccines by GPO includes tetanus antitoxin and live flu (H5N2) vaccine, which are licensed to be used in a pandemic situation. After the bird flu outbreak in 2004, the Flu vaccine plant was initiated by the government in 2007 with 1.41 billion Thai Baht in government funds allocated, matched by the World Health Organization and totalling US\$8.72 million (or 290.3 million Thai Baht).⁽²²⁾ The project aimed to manufacture up to 10 million doses of seasonal flu vaccine and was originally due to open in 2013. However, faced with construction and technical problems, factory design and other issues, the project was long-delayed and is expected to be in full operation in 2020. The price of flu vaccines produced by GPO will start at 200 Thai Baht per dose, which is higher than the cost of imported vaccines. The GPO stated that the economies of scale of current production capacity led to the higher price. The GPO also has other vaccines in the research and development stage including inactivated Zika vac in Vero cells, inactivated flu 4 strains in eggs and inactivated pandemic flu in Madin-Darby canine kidney (MDCK) cell.

In 2019, the GPO started to expand their biologics pipeline from vaccines only to proteins drugs. The Chulabhorn Research Institute, PTT Plc. and the GPO signed a cooperation agreement on the research and development of biologics.⁽²³⁾ Prototype of biosimilar Trastuzumab was the first product to be translating from research scale at Chulabhorn Research Institute to an industrial scale. Trastuzumab, under this collaboration, is currently undergo comparability exercise studies as per the guidelines on biosimilar monoclonal antibodies.

GPO Merieux Biological Products Co. Ltd. (GPO-MBP), established in 1996 by the GPO, Sanofi Pasteur and the Crown Property Bureau (Thailand), is the first joint venture between a public and private pharmaceutical company in Thailand. In 2001, GPO-MBP started with Vero rabies vaccine and hepatitis B vaccine as their first two products in Chachoengsao province, Thailand. MMR, influenza and DTP-Hb vaccines were later marketed by GPO-MBP in 2003, 2005 and 2007, respectively.⁽²⁴⁾ Currently, MMR and DTP-Hb are no longer available on the market due to outdated production technology compared with other MMR vaccines in the market, and the DTP-Hb bulk product supply was discontinued (as bulk product suppliers shifted toward a production of a combined DTP-Hb vaccine). In 2007, GPO-MBP with Acambis, USA and Sanofi Pasteur successfully co-developed a recombinant chimeric Japanese encephalitis virus vaccine from research scale to industrial scale. The product was launched in 2010 with Thailand as the product's country of origin. The chimeric JE and MMR vaccine produced by GPO-MBP was WHO prequalified in 2011 and 2014. The product is currently listed in Thailand's EPI programme and is exported to more than 17 countries around the world. Most productions at GPO-MBP are from bulk vaccines where GPO-MBP formulate, sterile filter, fill, freeze dry, label, test and release the finished dosage forms. Since many products are discontinued, GPO-MBP currently produces flu vaccines, JE vaccines and Vero rabies vaccines.

BioNet-Asia

BioNet-Asia is a Thai-French privately held biotech company focusing on the research and development, manufacturing and supply of vaccines. Granted

patents for the construction of *Bordetella pertussis* strains obtained by recombinant DNA technology from Mahidol University, BioNet successfully launched two products of monovalent recombinant acellular pertussis vaccines and combined tetanus, diphtheria and cellular pertussis (Tdap) vaccine in 2016.²⁵ The first product is more potent and requires a much lower dose of active ingredient of recombinant pertussis in the final vaccine than conventional chemically-inactivated pertussis toxin vaccines. Apart from acellular pertussis, BioNet has also at least ten products in R&D and clinical stages, including vaccines and recombinant proteins such as CRM197 protein carrier which is a carrier protein in conjugate vaccines, dengue and hepatitis B vaccines. The company has also developed and transferred the technology to produce Hib meningitis vaccines to other manufacturers, which commercialize as a pentavalent vaccine in Asia; for example, PentaBio, a pentavalent vaccine produced by Bio Farma in Indonesia.

Siam Biosciences

Established in 2009, Siam Bioscience is 100.0 percent owned by the Crown Property Bureau Equity Company and collaborates with the private sector and Mahidol University.⁽²⁶⁾ The company started the construction of its production facility in 2011 and had the Pharmaceutical Inspection Co-operation Scheme (PIC/S) certified with products commercialized in 2015. Currently, Siam Biosciences manufactures erythropoietin for anaemia and filgrastim for neutropenia. In 2017, Siam Bioscience expanded its business further by establishing its joint venture company with Cuba-based Centre of Molecular Immunology.⁽²⁷⁾ This has the purpose of research and development, manufacturing, and commercialization of mammalian cell

culture-derived biopharmaceuticals for treatment of various diseases such as cancer, autoimmune diseases and anaemia, with a focus on exportation. Construction of the plant, located in Nonthaburi, Thailand, is expected to be completed with six products launched in 2020.

National Biopharmaceutical Facility (NBF)

The Facility was initiated in 2008 under a collaboration between BIOTEC/ National Science and Technology Development Agency (NSTDA) and King Mongkut's University of Technology Thonburi (KMUTT).⁽²⁸⁾ The facility consists of two production facilities for microbial fermentation and cell culture. NBF also have downstream processing capabilities and an automatic sterile fill and finish line. These were all designed to comply with international GMP standards and biosafety regulations. The facility has a license from the Thai FDA to manufacture drugs, vaccines and biologics. Currently, NBF provides contract research and manufacturing services (CRAMS) as well as providing scale-up study for biopharmaceutical products. In 2019, NBF signed a memorandum of understanding with private biotech company from South Korea on their joint venture company KinGen BioTech (KGBio) aiming to be the contract manufacturing facility for biologics in the country.⁽²⁹⁾

Initiatives on research and development of Advanced Therapy Medicinal Products (ATMPs): The first ATMP product approved in the European Union (EU) and in the United States came in 2009 and 2010, respectively. Globally, ATMPs are still at an early stage and the number of patients treated with ATMPs is very low comparing with traditional biologics. ATMP's efficacy and the fact that it can treat some diseases where conventional approaches are not

effective create interest in industry, universities and research institutes for the research and development of ATMPs globally. In Thailand, several initiatives have started research and development of ATMPs including cancer immunotherapy excellence centre at Chulalongkorn University in which cellular therapy such as CAR T Cell, and allogeneic Natural Killer (NK) cell therapy are under research and development. A pilot clinical study on NK cell therapy has already been done in at least ten patients with promising results. Also undergoing clinical trial phase I studies, two studies of gene therapy in patients with transfusion-dependent β -Thalassemia were done at Ramathibodi hospital, Mahidol University, also show beneficial results.⁽³⁰⁾

Establishment of National Vaccine Institute (NVI)

The fragmentation of national work on vaccines, including R&D, led to the establishment of the National Vaccine Institute (NVI). The Thai NVI was officially established in 2012 as a public organization under Royal Decree. The NVI is a Thai public autonomous authority that coordinates vaccine affairs with domestic and international stakeholders. Its mission is to: drive and develop national vaccine policy and strategic plans; promote the nation's capacity through the development of human resources and infrastructure for vaccine research, development and production; build a collaborative network among vaccine experts and professionals domestically and internationally; and generate and manage vaccine information and technology. The NVI's ultimate goal is to lead Thailand towards vaccine security and self-reliance for vaccines in Thailand, including routine vaccines and vaccines for emergency situations. In 2019, the National Vaccine Security Act B.E.2561

was put in place with the aim for Thailand to be self-reliant on vaccines and for Thai citizens to have access to necessary immunization.⁽³¹⁾

Discussion

Our review found several developments in the Thai biologic drug system. The regulatory framework has been developed to make sure that biological products are well regulated, and that patients will receive safe, effective and good quality biologics. With the development of the Cell Therapy Act, Thailand will have the complete regulatory framework for biologics similar to USFDA and European Medicines Agency (EMA). Access to biologics is still however an issue especially for novel protein biologics and ATMPs, since these interventions are still very expensive. Vaccines are of interest to policy makers, particularly the issues of vaccine shortage and vaccine security especially for region-specific infectious diseases such as dengue, and pandemic preparedness such as influenza, zika and Ebola.

In an effort to lower drug expenditure, improve patient access to biologics and boost Thailand's economic growth, the biologics industry becomes a focus for the Ministry of Public Health and other national level policymakers. Progress has already been documented in this review but still there is still much to be done to improve patient access to biologics. To date only rituximab biosimilar is marketed by a local Thai biotech company called Siam bioscience. To accelerate the success of local biotech companies, a range of government policies should be implemented in order to align with the main policy, which promotes the biotech industry. First of all, the national regulatory framework must support local research and develop-

ment for biologics, however this should not compromise the quality, safety and efficacy of the product. National regulatory authority should establish fast-track channel to facilitate approval of local biotech manufacturer including availability of competent regulators to give advice to accelerate a successful marketing authorization of the new biologic or bio-similar. Providing consultation by competent regulator with regard to regulatory science may be necessary for local R&D to move from bench to bed side.

The development of the Cell Therapy Act should also be clear about which ATMPs will be included. Otherwise, overclaimed ATMPs that are not supported with scientific evidence will be more likely to occur, similar to what happened in the USA and Europe. Other policies to support investment in the biologics industry should be revised to match the nature of biologics research and development, which takes on average seven to ten years, such as a tax exemption time frame and the Board of Investment of Thailand (BOI) benefits. Several of these initiatives have already been started by the National Vaccine Institute. Public-private partnerships and joint ventures have been used as key collaborations to transfer advance biotechnology from developed countries and are expected to be the mainstream of technology transfer. More of these are anticipated to take place. Lastly, the development of the biotech industry should not be focused only on the research and development of the product itself but should also include the development of ecosystem of the product development (for example, the availability of an animal study centre that matches with the requirements of animal testing for biologics, , the qualified GMP compliance of laboratory testing with advanced technology for characteri-

zation and quality control of biologics, the qualified institute for collection of seed lot or cell bank specific for supporting manufacture of vaccine for local - communicable disease) and the overall health technology management concept (for example where researchers and developers' needs match the needs of the end users, in many cases health care payers).

In parallel, local biotech manufacturers should also apply lessons from other successful biotech cases such as taking Korea as their case study. In the age of digital disruption, the digital transformation of these manufacturing organizations is unavoidable in order to accelerate innovation within the industry. Several biotech start-ups have been initiated in Thailand mostly within universities as small businesses applying deep technology is becoming a global movement.

Even though some biotech companies have successfully commercialized their products, it was found that the government policy does not fully support the commercialization of these products. Some of these products, even though already listed on the NLEM or EPI programme, were not procured due to the higher price compared with products from other countries. It should be noted that the biologics and vaccine industry requires economies of scale to be viable, meaning that higher use of products leads to lower costs of production. Without support from the government, it is difficult for these manufacturers to thrive. One strategy to increase the scale of production is to improve the quality to meet international standard such as getting WHO pre-qualification in order to meet the requirement from international donor like Global Alliance for Vaccines and Immunisation (GAVI) and United Nations International Children's Emergency Fund (UNICEF) for vaccine tender. If

quality standard can meet UN requirement, the local manufacturing can access to big market in order to increase the scale of production with decreased cost of production and further reduction of the vaccine price. Local pharmaceutical price control, currently undertaken by the Thai government, should be balanced against the profit the industry can make to invest in new product research and development. As biosimilar research and development requires clinical trials even though lesser than what is required for the reference product, studies have shown that the price of biosimilar biologics would drop by only 30.0% compared with its reference product. In 2016, Thailand developed an innovation list of novel products and services invented in Thailand which once on the list, are entitled to the benefit of the government procurement programme for the maximum 8 years.⁽³²⁾ The biologics and biosimilar products that were researched and developed in the country could also be on this innovation list.

The manufacturer itself should also consider exporting to other countries to help reach economies of scale. Therefore, a requirement for manufacturers to export is an important factor that should also be supported by the government; for example, introducing regulatory standards as well as health care markets and patient access system that match those in different countries which are the target countries for exporting of biologics locally produced in Thailand, as well as global quality standard such as the WHO pre-qualification process.

A short-term strategy to improve access to biologics is to use an innovative financing model; for example, the use of Managed Entry Agreements

(MEAs). These agreements can be used for high-cost biologics products that are cost-ineffective or doesn't have enough evidences, but patients have unmet medical need. Previously, several MEAs have been implemented for example, the reimbursement of imatinib where Max Foundation provided free imatinib to UCS patients.⁽³³⁾ With these agreements, the risks are shared among payers and the manufacturers. Other tools include patient cost-sharing, revising the reimbursement list to cover first-on drugs that are for patients with life-threatening diseases and who have unmet medical needs.

At last, human resources should be developed for every sector along the value chain of the biologics drug system. Currently, only a few hours of biologics and vaccine topics are included in the Doctor of Pharmacy programme in most pharmacy schools in Thailand. The existing workforce should also be reskilled as these topics were not included in the previous curriculum either. The field should not be limited to the research and development of biologics but also focus on regulatory sciences from both a regulator and manufacturer perspective. The workforce at the hospital level where knowledge about the quality of biologics is needed in order to select and procure the product should also be supported. Lastly, the clinician as well as health care providers should have a better understanding of the differences of these products, compared with chemical small-molecule pharmaceuticals in order to prescribe the drug effectively for the benefit of the patient. Increased understanding of these biological drugs will improve the high confidence to make substitution of biosimilar for reference product to help decrease expenditure of high price reference

product without impaired quality standard and clinical outcome. Furthermore, improved knowledge of biological drugs will help establish effective drug management to reduce the specific risk and abuse related to this type of drugs.

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บทคัดย่อ: สถานการณ์ระบบยาชีววัตถุในประเทศไทย

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ยาชีววัตถุเป็นนวัตกรรมทางสุขภาพซึ่งเปลี่ยนแปลงแนวความคิดการรักษาพยาบาลโรคหลาย ๆ ชนิด อย่างไรก็ตาม ยาชีววัตถุมีคุณลักษณะสำคัญที่เป็นเอกลักษณ์เฉพาะซึ่งส่งผลกระทบต่อระบบยาของประเทศโดยรวม การศึกษานี้มีวัตถุประสงค์เพื่อวิเคราะห์สถานการณ์ยาชีววัตถุในระบบยาของประเทศไทย ผลการวิเคราะห์พบว่าประเทศไทยมีการพัฒนาระบบการควบคุมกำกับดูแลยาชีววัตถุของประเทศจนในปัจจุบันมีความทัดเทียมกับมาตรฐานสากลขาดแต่เพียงกฎหมายที่ใช้ในการกำกับดูแลผลิตภัณฑ์เซลล์บำบัดซึ่งกำลังอยู่ระหว่างการดำเนินการ อย่างไรก็ตามพบว่ายาชีววัตถุเหล่านี้ถึงแม้ว่าได้รับอนุมัติทะเบียนแต่การเข้าถึงยังมีจำกัดเนื่องจากส่วนใหญ่มีราคาสูง การเพิ่มขีดความสามารถในการวิจัยและพัฒนายาชีววัตถุเพื่อออกสู่ตลาดโดยผู้ผลิตในประเทศเป็นกลไกหลักที่รัฐบาลไทยใช้เพื่อลดค่าใช้จ่ายด้านสุขภาพ เพิ่มการเข้าถึงและเพิ่มการส่งออกไปยังต่างประเทศเพื่อเพิ่มรายได้ของประเทศ กลไกทางด้านราคาแบบใหม่ ๆ จึงเป็นกลไกที่ใช้ระยะสั้นเพื่อเพิ่มการเข้าถึงยาชีววัตถุเหล่านี้ การกระจายยาชีววัตถุของประเทศไทยพบว่ามีมาตรฐานภายใต้การกระจายวัคซีนของประเทศ อย่างไรก็ตามการพัฒนาบุคลากรที่มีความรู้ด้านชีววัตถุเป็นสิ่งสำคัญที่รัฐควรริบดำเนินการเพื่อทำให้ระบบยาชีววัตถุโดยรวมมีประสิทธิภาพ

คำสำคัญ: ยาชีววัตถุ, วัคซีน, การเข้าถึง, การวิจัยและพัฒนา, การแพทย์ส่วนบุคคล