Introduction to the Biopharmaceutical Industry

KINGEN BIOTECH

Agenda

- What are biopharmaceutical products
- Enabling technologies in the Biopharmaceutical and Vaccine industries
- Transformation of the pharmaceutical industry
- Existing manufacturers in Thailand

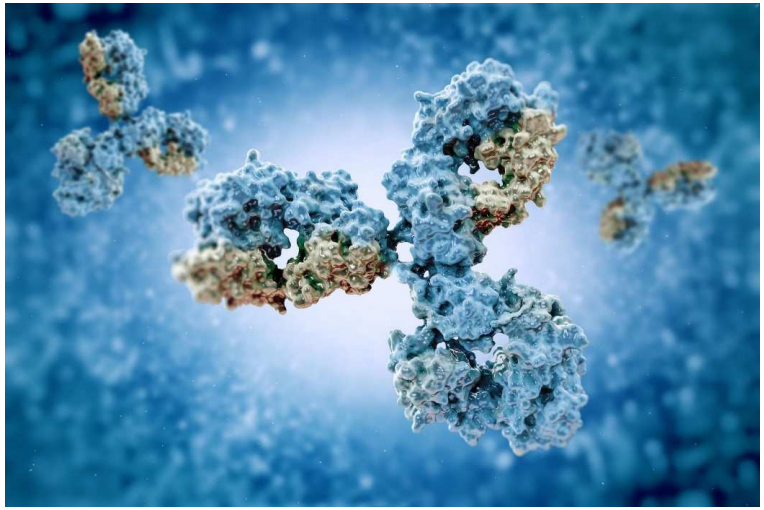
What are biopharmaceutical products?

Background

- **Biological/biopharmaceutical products** can be composed of **sugars, proteins, or nucleic acids, or a combination of these substances**. They may also be **living entities, such as cells and tissues**. Biologics are made from a variety of **natural resources—human, animal, and microorganism**—and may be produced by **biotechnology methods**. (USFDA)

Drug	Size (atoms)	Known Goods	Size (pounds)
Aspirin	21	Bicycle	~20
Somatotropin	~3,000	Automobile	~3,000
Trastuzumab	~25,000	Business jet	~30,000

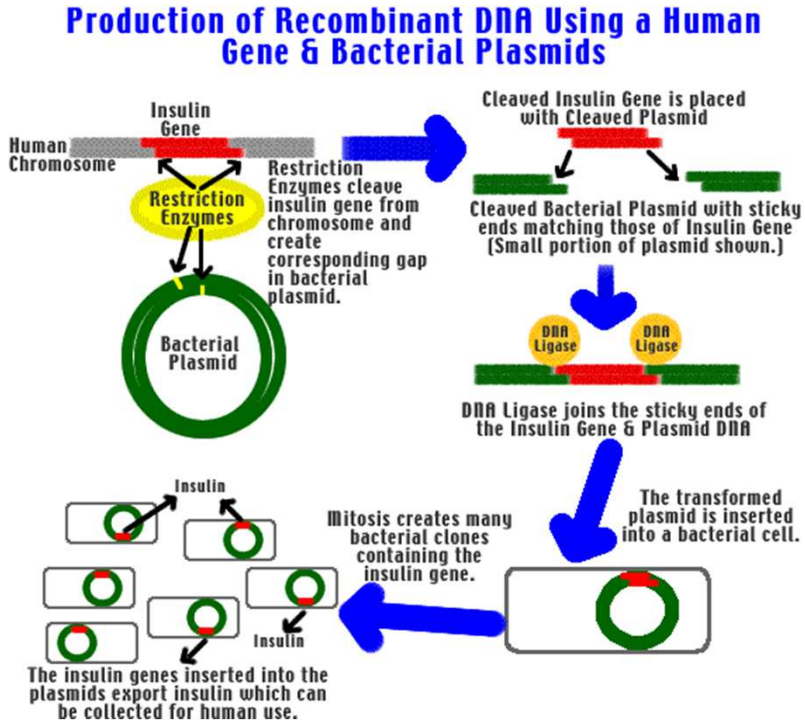
Source: *From Science to Operations: Questions, Choices and Strategies for Success in Biopharma.* Otto R, Santagostino A, Schrader U, Eds. McKinsey & Company: New York, NY, 2014.



Source: ccabcanada.com

Recombinant technologies

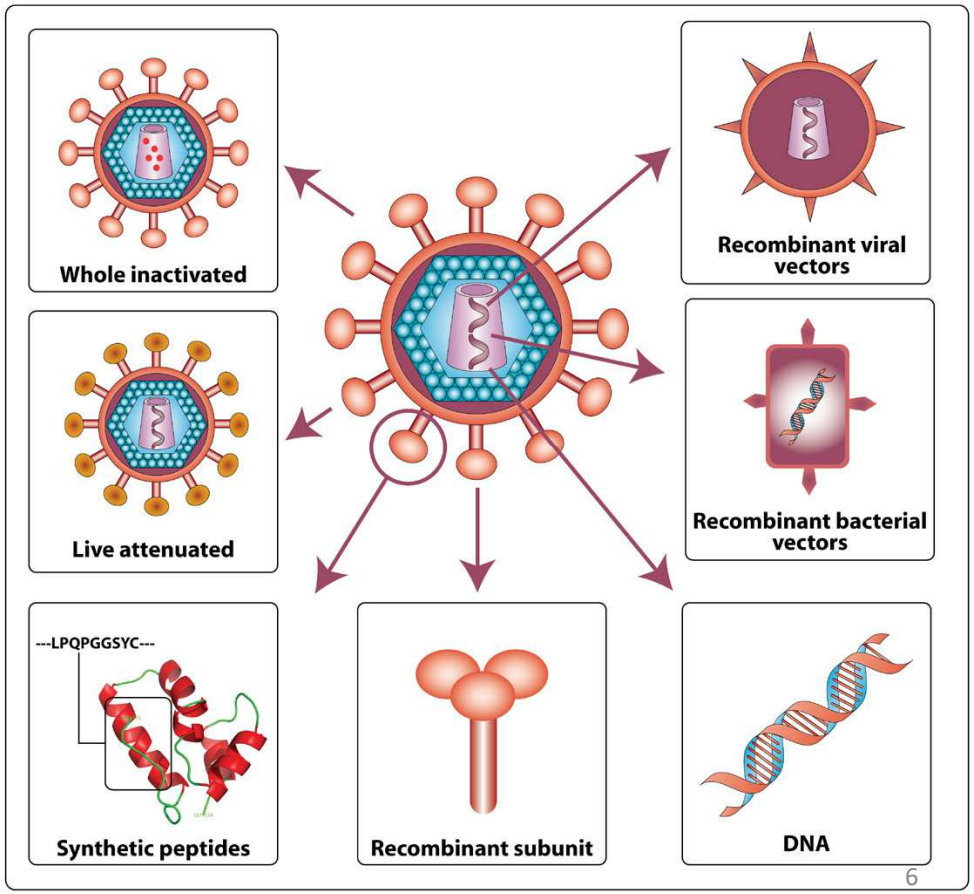
- Proteins produced through means of biotechnology/genetic engineering
  - Human proteins expressed in microorganisms or cell cultures
  - Examples: EPO, GCSF, Interferons, Streptokinase, growth factors, etc.



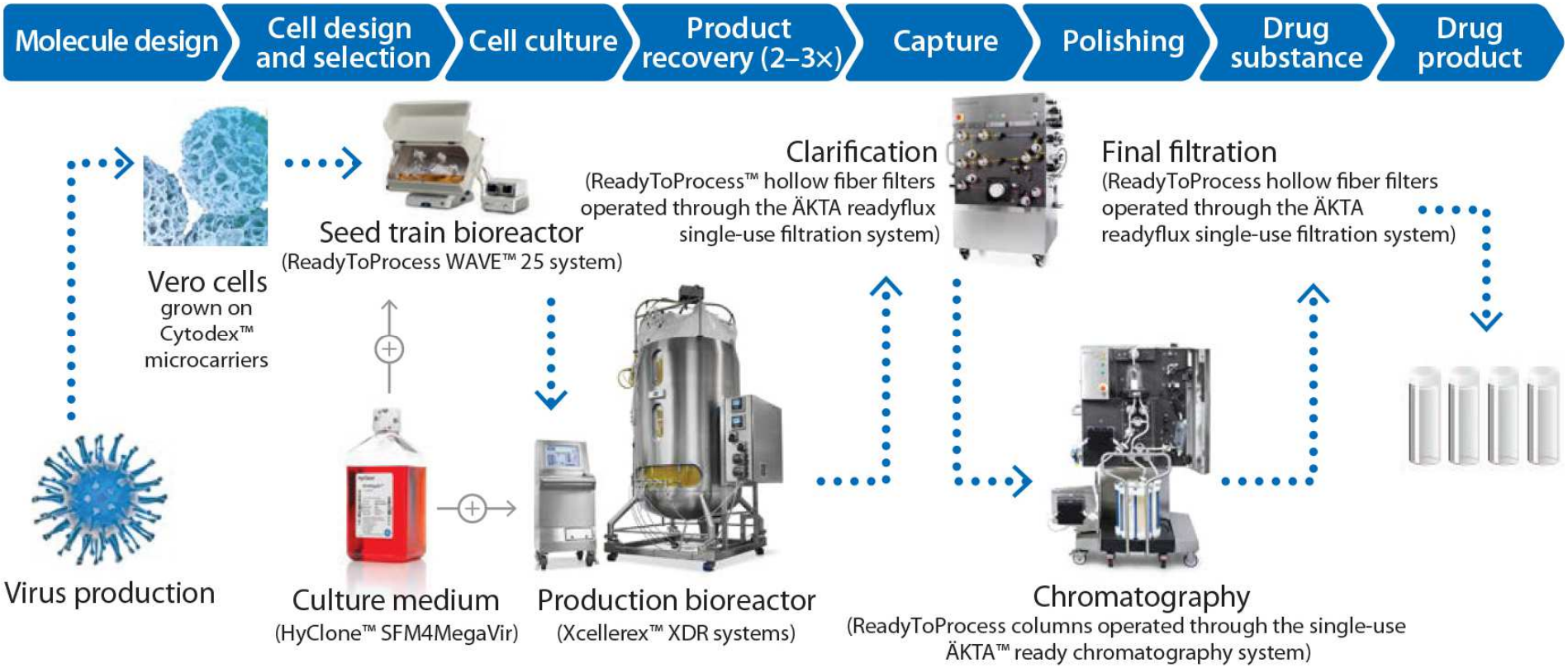
Source: science.halleyhosting.com

Main platform technologies for vaccines

- Bacterial vaccines
  - Whole cell vaccines
  - Inactivated vaccines
  - Recombinant bacterial vectors
- Viral vaccines
  - Live-attenuated vaccines
  - Inactivated vaccines
  - Recombinant viral vector vaccines
- Recombinant Proteins
  - Sub-unit vaccines
  - Virus-like particle
- DNA and RNA vaccines
- Liposomes



How to produce vaccines?



Source: Bioprocess International, Flavivirus Vaccine Production Accelerates with Modern Bioprocess Tools and Solutions, Nov 2017

Enabling technologies in the Biopharma and Vaccine industries

How do we produce biopharmaceuticals and vaccines?

Virus manufacturing facility

- Mostly biosafety level >2
  - Biocontainment
  - Negative pressure quite common
  - Personnel protection (PPE, proper training, etc.)
- Contamination issues
  - How to prevent contamination to the environment
    - Waste decontamination
  - How to prevent contamination among the product
    - Change over/Cleaning validation/ disposable technologies

Source: vaccinews.net

Protein and DNA manufacturing facility

- Mostly Biosafety level 1
  - Less risks for personnel and environment
  - Management of recombinant DNA and cells required
- High level of expertise from personnel expected
- High investment costs
- High technological barriers

How to produce rProtein and DNA vaccines?

Source: MoBiTec GmbH

Source: BioPharma-reporter.com

Manufacturing Technologies #1

- Upstream processing
  - Bioreactors

Source: infors-ht.com

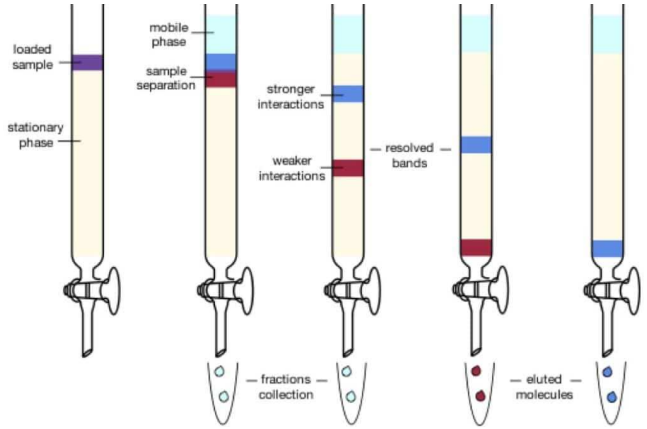
Source: cellculturedish.com

Source: celltrion.com

Manufacturing Technologies #2

- Downstream Processing
  - Purification
    - Chromatography
    - Filtration

Source: biotech.pall.com



Source: bitesizebio.com

Source: gelifesciences.com

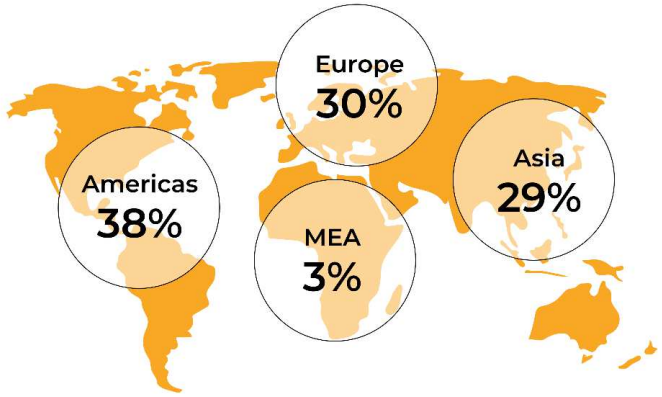
Summary: Main vaccine manufacturing technologies

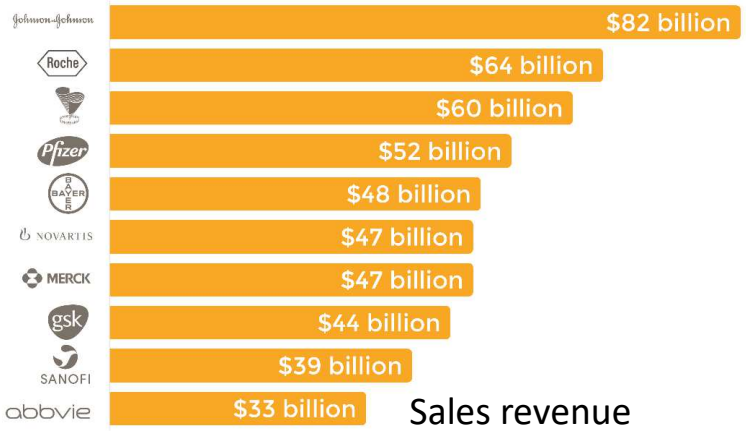
- Upstream processing
  - Eggs
  - Carbohydrate conjugation
  - Fermentation
  - Cell culture
  - Oligonucleotide synthesis
- Downstream processing
- Fill and finish

Source: Merck-Millipore.com

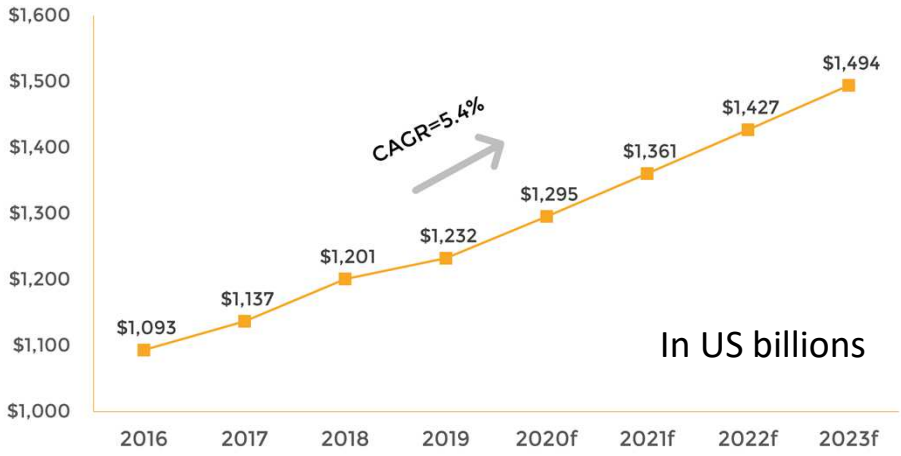
Transformation of the pharmaceutical industry

Global pharmaceutical market in 2020s





Sales revenue



In US billions

https://www.thepharmamarketer.com/post/global-pharmaceutical-market

LARGEST PHARMACEUTICAL* COMPANIES

in the World by Market Cap

*The source provides a list of healthcare companies that work closely with pharmaceuticals, including biotech, pharmaceutical retailers, clinical laboratories, etc.

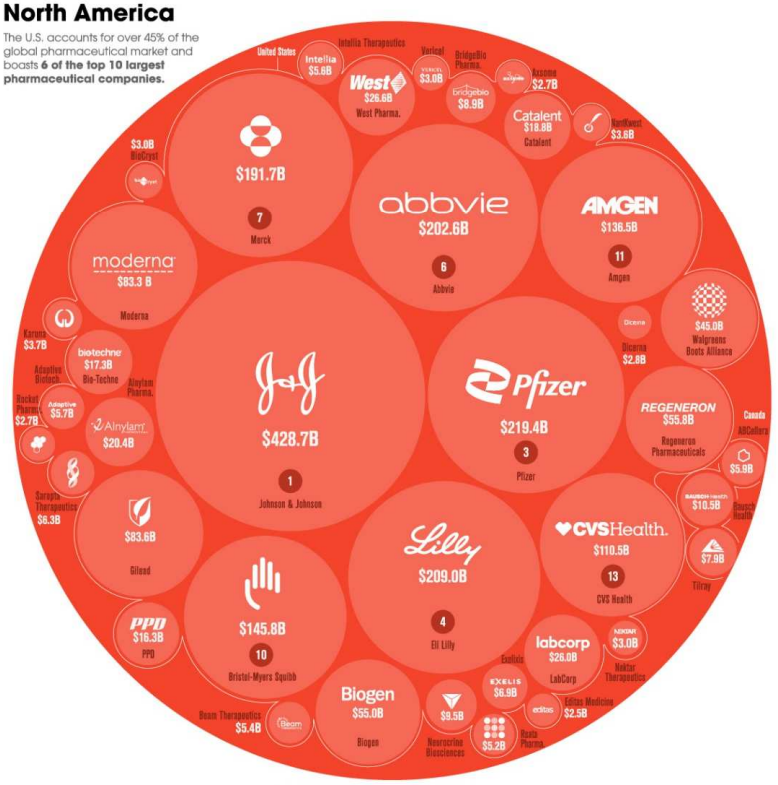
The global pharmaceutical industry is expected to witness positive growth as the top pharma companies are at the forefront of the fight against COVID-19.

As 2020 progressed, drugmakers battled the coronavirus on the one hand and, on the other, contended with pandemic disruptions. How did they fare at the end of it all?

From Johnson & Johnson to Editas Medicine, we map the biggest pharmaceutical companies based on their market cap value.

North America

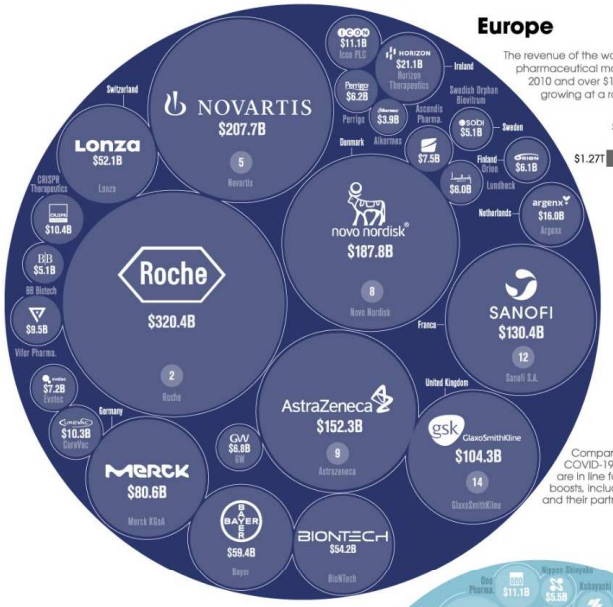
The U.S. accounts for over 45% of the global pharmaceutical market and boasts **6 of the top 10 largest pharmaceutical companies.**



Europe

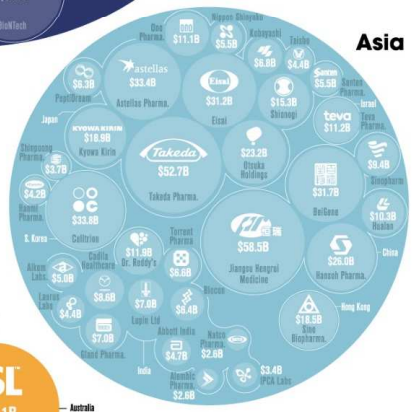
The revenue of the worldwide pharmaceutical market was $888.2B in 2010 and over $1.27T at the end of 2020, growing at a rate of 4.2% per year.

Source: Statista



Companies with successful COVID-19 drugs and vaccines are in line for significant revenue boosts, including Pfizer, Moderna, and their partnerships.

Asia



Jiangsu Hengrui Medicine, Asia's largest pharmaceutical company, is China's market leader in oncological treatments, where demand is ever increasing.

Oceania

Brazil, India, Russia, Colombia and Egypt are the biggest emerging markets for pharmaceutical revenues.

Source: Companies Market Cap. All data as of 23rd June 2021

VISUAL CAPITALIST

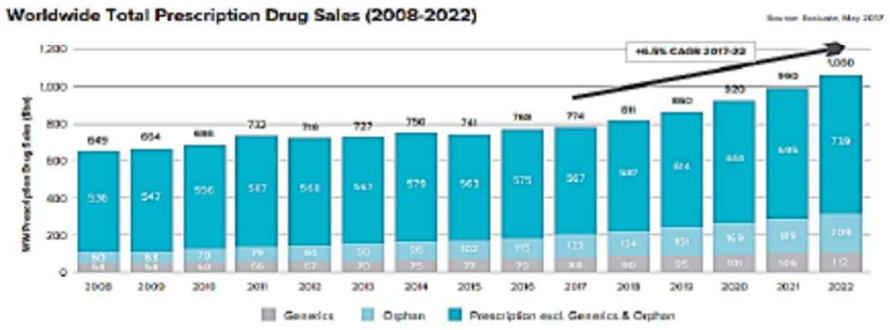
/visualcapitalist @visualcap visualcapitalist.com

COLLABORATORS RESEARCH + WRITING Anshool Deshmukh and Raul Amoros | DESIGN Rosey Eason

Regional pharmaceutical market

2017 Pharmaceutical Market

Global	**$ 774bn**
>Original	$ 690bn
>Generic	$ 84bn
CAGR 2017 – 2022	6.5%
Africa, Asia (excl. Japan)	17%
Estimated 2022	
Global	$ 1.06trn



Country	US$bn 2012	US$bn 2013	US$bn 2014	US$bn 2015	US$bn 2016	US$bn 2017
China	80,1	94,1	108,2	123,2	138,1	152,8
India	18,0	19,8	22,0	24,4	27,1	30,1
South Korea	15,8	16,9	18,0	19,0	20,1	21,1
Indonesia	6,7	7,3	8,0	8,7	9,5	10,3
Taiwan	5,2	5,5	5,7	5,8	5,9	6,1
Thailand	4,4	4,7	4,9	5,2	5,5	5,8
Vietnam	2,9	3,3	3,9	4,4	5,1	5,7
Philippines	3,0	3,1	3,3	3,4	3,6	3,8
Malaysia	2,0	2,1	2,3	2,5	2,7	2,8
Hong Kong	1,3	1,4	1,5	1,6	1,7	1,8
Singapore	0,7	0,8	0,8	0,9	1,0	1,0
Total	140,2	159,2	178,5	199,2	220,1	241,4

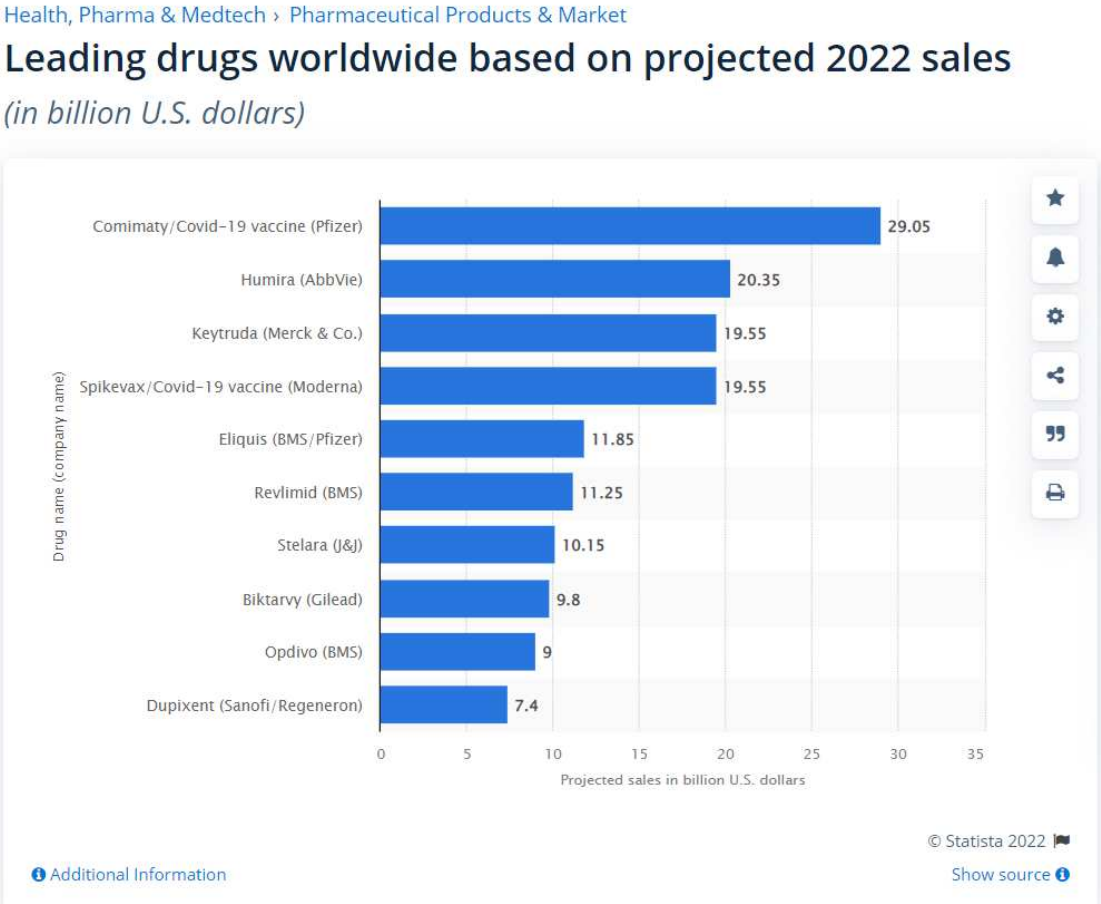
Thailand Pharmaceutical market in 2017

Total Market	$ 5.8bn
Import	$ 1.5bn
Export	$ 0.37bn

CAGR 2017 – 2021 **6.0%**
Estimated 2022

Best selling drugs in 2022 (projection)

- Rise of biopharmaceuticals and vaccines
  - **Drug products derived through biotechnology** instead of chemical synthesis
  - Offer unprecedented cures to diseases including tumors, cardiovascular, autoimmune and other metabolic diseases
  - 13 of Top 20 drugs in 2018 were biopharmaceuticals and vaccines
- Most biopharmaceuticals are expensive!
  - NHSO cannot afford all biopharmaceutical drugs
  - Low access to biopharmaceuticals amongst Thai population
  - High dependency on imported products with only few manufacturers in the country
- Thailand currently is not recognized as a relevant player in the global biopharmaceutical and vaccine value chain!

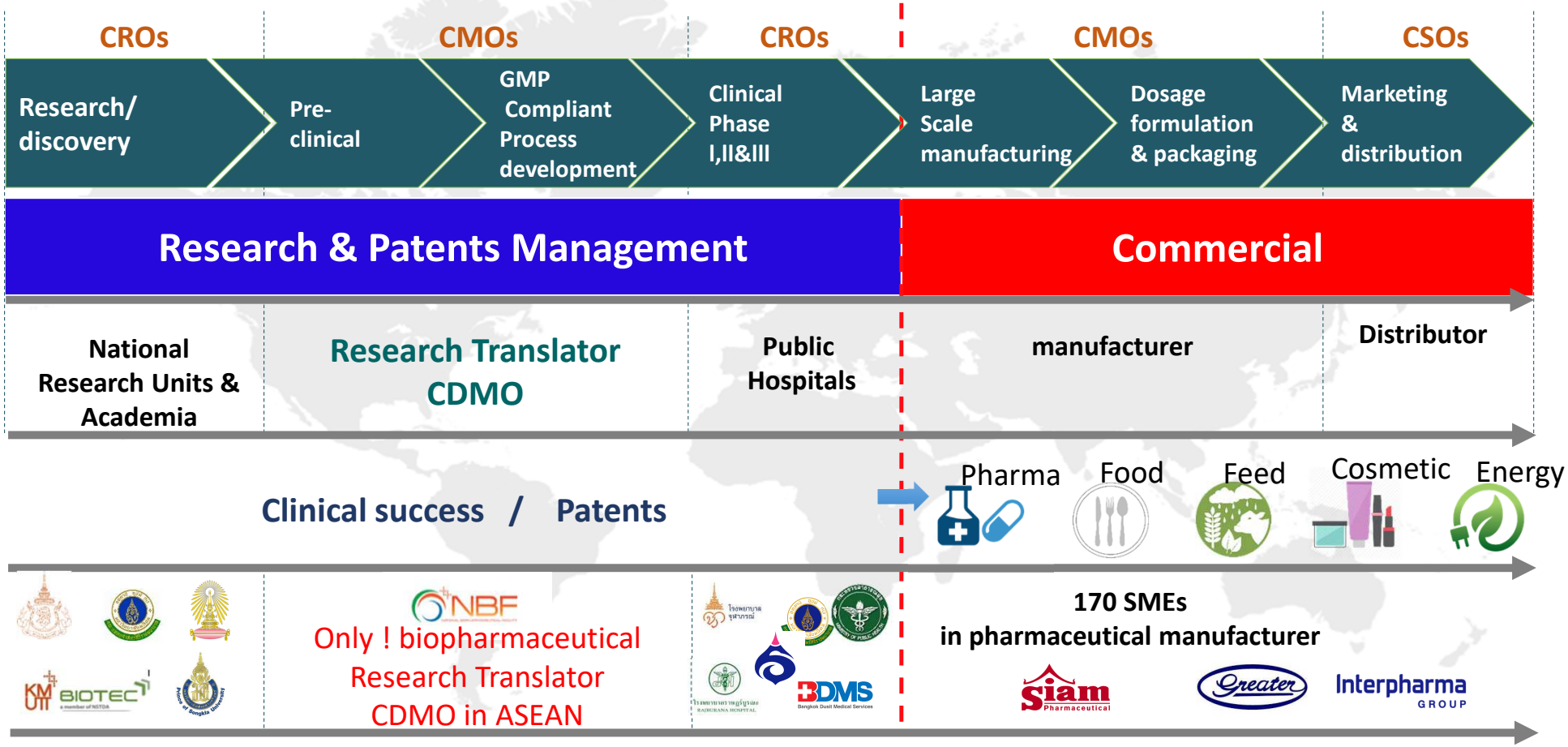


Structure of the global pharmaceutical market:

- Pharmaceutical companies were classified into three main categories:
  - **Big Pharma:** which develop new chemical entities (small molecules)
  - **Biotechnology companies** which develop biologicals products
  - **Generic companies** which develop bioequivalent products of the research bases companies

https://www.thepharmamarketer.com/post/global-pharmaceutical-market

BIOPHARMACEUTICAL SUPPLY CHAIN



CROs = Contract Research Organizations
CMOs = Contract Manufacturing Organizations
CSOs = Contract Sales Organizations

KINGEN BIOTECH

Pharm. industry transformation

- Pharma companies becoming biotechnology-based companies
  - Roche + Genentech
    - 17 approved products
  - AbbVie + Allergan
    - Allergan's Botox, etc.
  - MSD
    - Vaccines, antibodies, animal health, etc.
- Biotech companies grow fast!
  - Gilead Sciences (est. 1981, revenue USD 26 billion)
    - Harvoni and Sovaldi
  - Amgen (set. 1980, revenue USD 22 billion)
    - Enbrel, Neulasta, Neupogen, Epogen, Aranesp, etc.

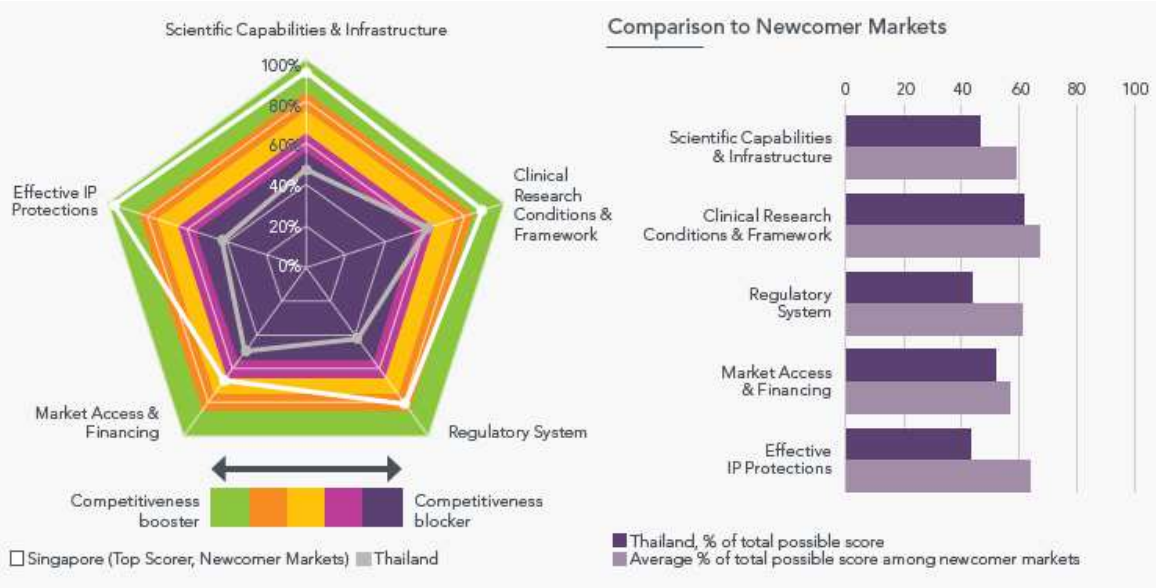
Biopharma market in Thailand and ASEAN

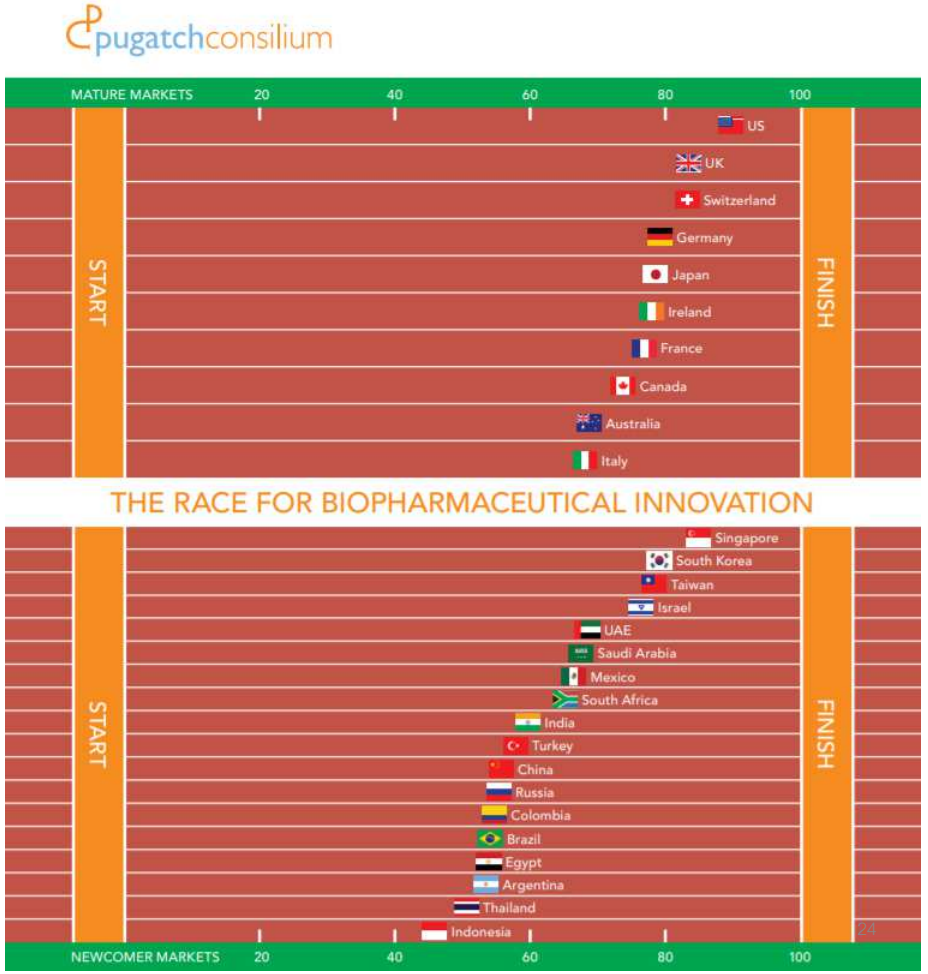
- Population: 70 million
- Biopharma market size USD 1 billion
  - Local manufacturers
    - Sanofi: Vaccines
    - Thai Red Cross: Vaccines and blood products
    - Bionet-Asia: Vaccines
    - GPO: Vaccines, mAbs (in planning)
    - SBS: EPO, PEG-GCSF, mAbs (construction completed)
- Largest contributor = National Health Security Organization (NHSO)
  - Universal Healthcare Coverage
  - 80% of total healthcare expenditure in Thailand
- Strongly regulated drug market
  - Drug price policy
  - National List of Essential Medicines
  - National List of Innovative Drugs
- Prioritization of local contents
  - 30% of healthcare budget set aside for local products
  - Local manufacturers strongly prioritized

- ASEAN
  - 600 million population
  - Harmonized drug registration
  - USD 50 billion biopharma market by 2023
- Manufacturers
  - Singapore
    - APIs
  - Malaysia
    - Insulin
  - Vietnam
    - Vaccines
  - Indonesia
    - Vaccines
    - Biophama
- Most manufacturers are state enterprises
  - Liberalization ongoing
- Life science start-ups scene mixed
  - Vibrant in Singapore
  - Intermediate level of activities in Thailand and Malaysia

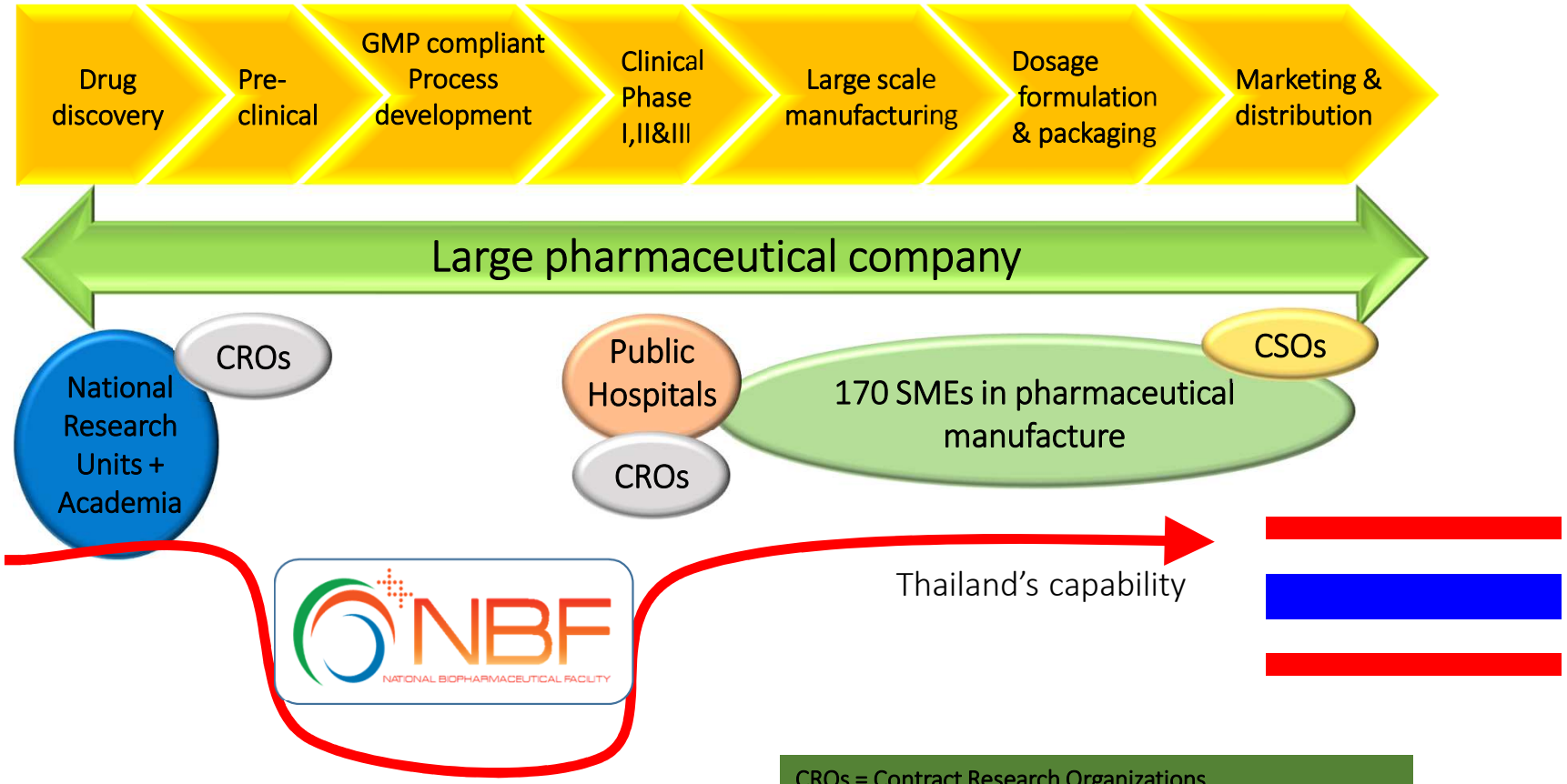
Low competitiveness

- Thailand has low competitiveness in biopharmaceutical industry and research landscape
  - Low scientific capabilities & infrastructure
  - Major flaws in regulatory system
  - Ineffective IP protections



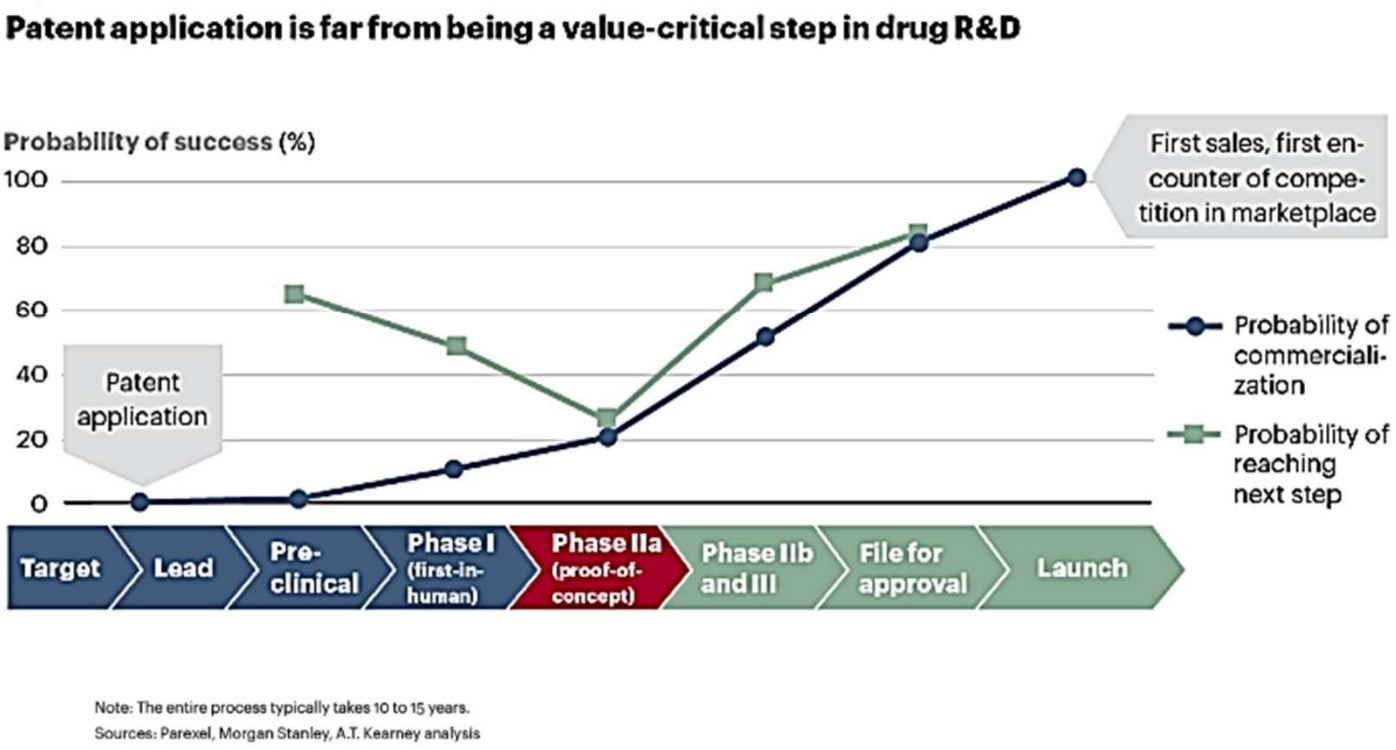


Pharmaceutical Value Chain



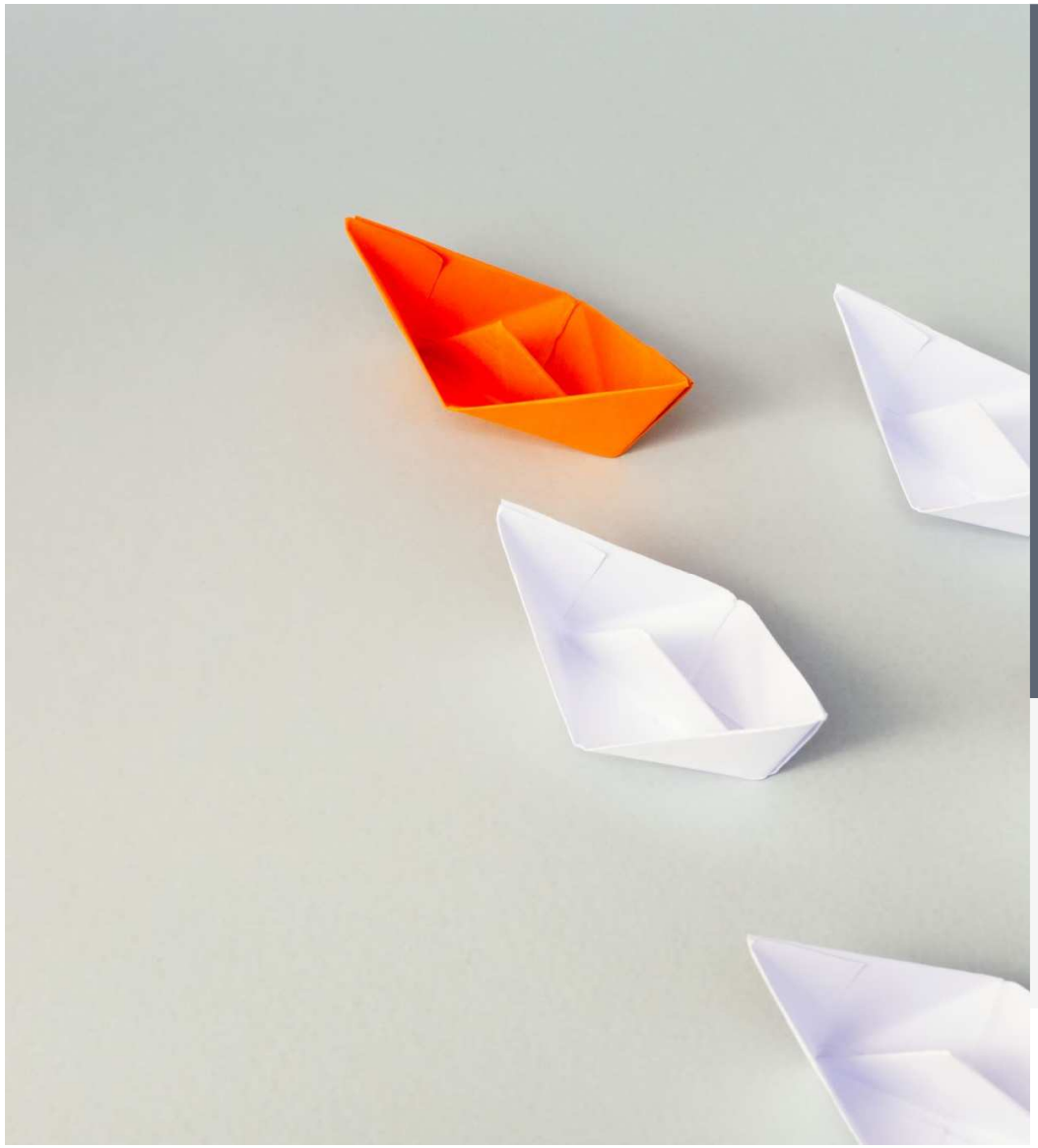
CROs = Contract Research Organizations
CMOs = Contract Manufacturing Organizations
CSOs = Contract Sales Organizations

CDMO



- Patent application not a guarantee for success in Biopharmaceutical business
- 1 out of 50,000 drug candidates will make it to the market
- Proof-of-concept studies required for pharmaceutical product development
- Probability of success increases significantly after Phase II clinical trials

→ Manufacturing of pharmaceutical products for clinical trials at a CDMO can mitigate the financial risks.



Existing manufacturers in Thailand

Notable manufacturers in Thailand

- Human vaccines
  - QSMI
  - GPO-MBP
  - Bionet-Asia
  - Greater Pharma
- Animal Vaccines
  - DLD
- Biopharmaceuticals/Biologics
  - Siam Biosciences
  - Thai Red Cross
- ATMP facilities
  - Austrianova
  - Chulalongkorn university
  - Genepeutic
- CDMO (Contract Development and Manufacturing Organization)
  - NBF by KinGen Biotech
  - (MU Bio)

Example of vaccine manufacturing capabilities in Thailand based on technologies

- Eggs
  - Government Pharmaceutical Organization (Influenza)
  - Department of Livestock Development (Newcastle, Avian flu)
- Fermentation
  - Queen Saovabha Memorial Institute, Thai Red Cross (BCG)
  - Bionet-Asia (Acellular pertussis)
  - KinGen Biotech (DNA vaccines, rProteins)
- Cell culture
  - Department of Livestock Development (Foot and Mouth Disease)
  - KinGen Biotech (Viral vaccines)
- Fill and finish
  - GPO-Merieux Biological Products

National Biopharmaceutical Facility

Biopharmaceutical Research Translator of Thailand

NBF was Thailand's first state-owned CDMO for production of clinical, research-grade biopharmaceuticals.

- GMP compliance for Biopharmaceutical products
- USD 40 M investment in facilities and infrastructure
- More than 100 scientists, engineers, pharmacists and technicians
- Fermentation 500 L & Cell culture 500L
  - pDNA, rProtein, Mabs, Viral vaccines
- Located in the Science and Industrial Park Bangkhuntien
- Managed by KinGen Biotech Co., Ltd.

Background

About Us

KinGen Holdings Stakeholder

Genexine

Innovative immunotherapeutic and next generation novel long-acting biologics

NBF NATIONAL BIOPHARMACEUTICAL FACILITY

Thailand's #1 cGMP capacity and CMC expertise

BGIC BIO GENETECH INTERNATIONAL CO., LTD.

Business expertise in South East Asia and execution capacity

Vision and mission

VISION:
To be ASEAN's No.1 CDMO for cutting-edge biopharmaceuticals and vaccines

MISSION:
To solve unmet healthcare needs of population in SEA with state-of-the-art Korean biotechnologies through R&D and manufacturing of new biopharmaceutical drugs

INTEGRATED BIOTECHNOLOGY BUSINESS PLATFORM

- To accelerate the development of the biotechnology industry in Thailand

INNOVATION PLATFORM

Technology Partnering, In/Out-Licensing

INCUBATION PLATFORM

Catalyst & IP Representation

IN-TO MARKET CONSULTING

Market Intelligence & Market Access to ASEAN

- Founded by Marvel and Novel Co., Ltd. and KMUTT foundation as a technology commercialization company
- Strong cooperation with government agencies, education and the private sector.

Genexine

- A clinical stage biotechnology company focused on the development and commercialization of innovative immunotherapeutics and next generation novel long-acting biologics.
- KOSDAQ: 095700 (Market cap: USD 2.5 billion)

Our goal

To bring to patients medicines that will transform their lives

MAKE INCURABLES CURABLE

Genexine is pioneering next generation biotherapeutics to treat and save the lives of patients with serious diseases.

Technology

hyFc technology

PLASMID DNA VACCINE

Innovative hyFc® Technology for Long-Acting Therapeutics

- drive the discovery of a wide range of differentiated protein therapeutics

pDNA Vaccine Technology: Immune Enhancing Technology

- Cervical cancer (therapeutic)
- COVID-19 (prophylactic)

Global Partners

ONE-STOP-SERVICE CDMO IN THAILAND AND ASEAN

UNLEASH THE TRUE POTENTIAL OF DRUG DISCOVERY TO IMPROVE THE QUALITY OF LIFE OF ASEAN PATIENTS

- cGMP compliant biotech CDMO facility
- One-stop-service: From drug substance production to fill & finish
- Experience in plasmid DNA, recombinant proteins, animal vaccines and monoclonal antibodies
- Biopharma Manufacturing Process Development and Tech Transfer
- Independent with robust access to academia
- Advanced technology to increase yield resulting in time and cost saving
- Regulatory Expertise: a strong track record of quality, compliance, and regulatory expertise

GMP Facilities

- **Unit 1-Microbial Bioprocess**
  - USP Fermentation: 500L
  - DSP Chromatography, TFF
  - BSL2-compliant
- **Unit 2-Cell Culture Bioprocess**
  - USP Cell culture: 500L,
  - DSP Chromatography, TFF
  - BSL2-compliant
- **Unit 2.1-Vial Filling Line** (2022)
  - Vial filling, 6000 objects per hour
  - Lyophilization (optional)
- **Unit 3-Versatile Filling Line** (2022)
  - Vials
  - Pre-filled syringes
  - Cartridges
- **Unit 4-Cell culture Bioprocess** (2022)
  - USP Cell culture: 2000L (Cytiva, disposable)
  - DSP Chromatography, TFF
  - BSL2-compliant

Unit 4: 2,000 litre cell culture

KINGEN BIOTECH

NBF
NATIONAL BIOPHARMACEUTICAL FACILITY

Biologic Testing &Viral vector Characterization

Protein characterization

Protein Identification for Virus Vector, MALDI-TOF/MS & Analytical Ultra Centrifuge

- Viral vector characterization/AAV Quantificatiom
- Nanoparticla

Next Generation DNA Sequencer

- Host-pathogen interaction
  - Human and pathogen genomics
  - Human and pathogen transcriptomics
  - Host immune responses (T and B cell diversity)
- Quality of vaccine stock
- Diversity of HLA polymorphisms in population
- Detection of new pathogenic strains

Multimode Microplate reader

- Microbial Growth/MIC
- IC50/LD50
- Endpoint ELISAs/EIA
- Colorimetric Protein Quantification
- Kinetic ELISAs/Enzyme Assays
- Bacterial Identification
- UV: DNA, RNA and Protein Quantification
- Cell viability & proliferation

Oligonucleotide quantification

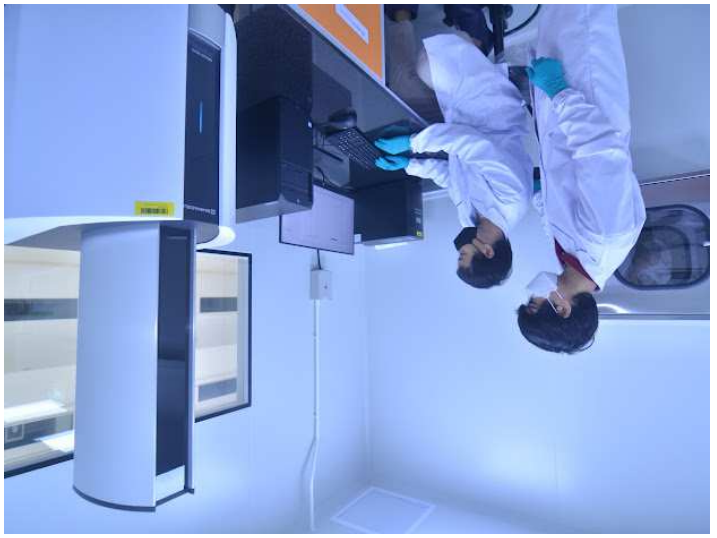
- DNA RNA Quantification
- Protein Quantification
- UV-VIS

Semi Dry blot, Electrophoresis

- Transfer Protein, DNA, RNA from gel to membrance

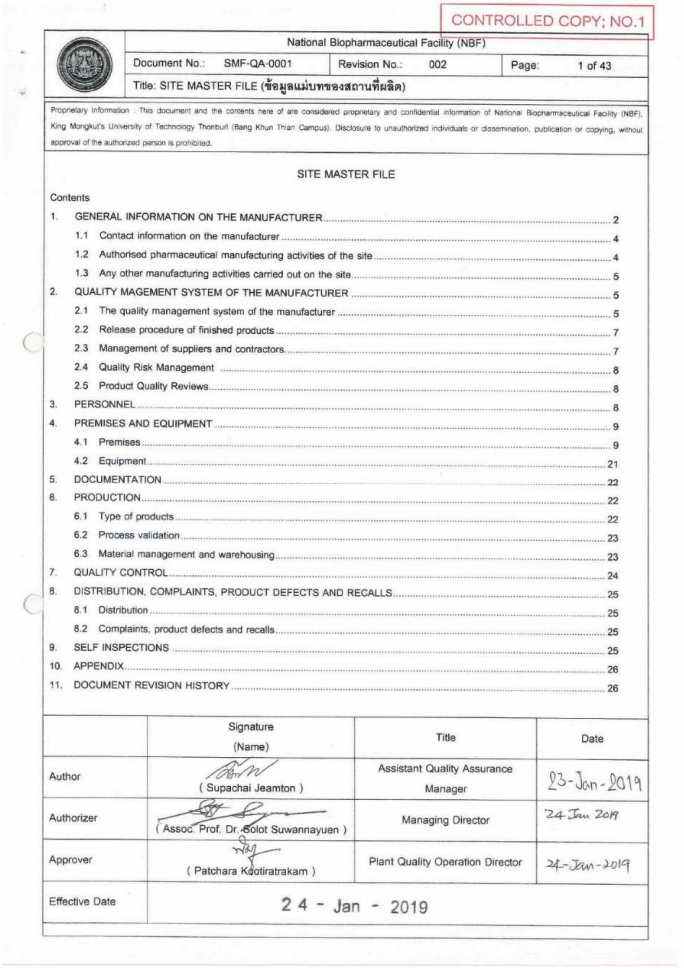
Gel Document System

- Specific and Unspecific Detection of Proteins and Nucleic Acids (DNA/RNA)
- Blot Imaging (Western/Northern/Southern & Variations thereof)
- Gel Imaging (Agarose/PAGE)
- Whole Organisms (basic in vivo imaging)
- Chemiluminescent, Fluorescent & Colorimetric Imaging



Quality systems in place

- Quality risk management
- Quality documentation management
  - SMF, SVMP, PM plan, SOP, WI, BMR, protocol, etc.
- Deviation and CAPA management
- Change control management and variation
- GMP, QMS and technical training management
- Self inspection & supplier audit
- Batch release/rejection and release to market
- Customer complaint & product recall management



CONTROLLED COPY; NO.1

National Biopharmaceutical Facility (NBF)

Document No.: SMF-QA-0001	Revision No.: 002	Page: 1 of 43

Title: SITE MASTER FILE (ข้อมูลแม่บทของสถานที่ผลิต)

Proprietary Information : This document and the contents here of are considered proprietary and confidential information of National Biopharmaceutical Facility (NBF), King Mongkut's University of Technology Thonburi (Bang Khun Thian Campus). Disclosure to unauthorized individuals or dissemination, publication or copying, without approval of the authorized person is prohibited.

SITE MASTER FILE

Contents

	Signature (Name)	Title	Date
Author	(Supachai Jeamton)	Assistant Quality Assurance Manager	23-Jan-2019
Authorizer	(Assoc. Prof. Dr. Solot Suwannayuen)	Managing Director	24 Jan 2019
Approver	(Patchara Kootiratrakarn)	Plant Quality Operation Director	24-Jan-2019
Effective Date	24 - Jan - 2019		

Examples

Genexine

- Manufacturing of MCB/WCB and DS for clinical use
- 4 Different plasmids
- Technology Transfer from Genexine, South Korea
  - Manufacturing technologies
  - Analytical methods
    - Product specific methods
    - Cell line assays
- 1 year project duration
- MFDS inspection expected
- DP to be produced at BINEX, South Korea

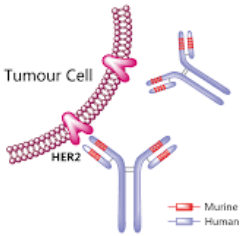
HEMAX™

BJC

BIOSIDUS

- Best selling EPO in Thailand
  - Treatment of anemia
- Localization of manufacturing steps from Argentina to Thailand
- Multi-stage collaboration
  - Repacking of finished product
    - Technology transfer initiated
  - Fill and Finish of EPO
    - Letter of Intent received
    - MOU under preparation
- Long-term anchor tenant
- FDA License issued in Aug 2020

CRI/WT-1



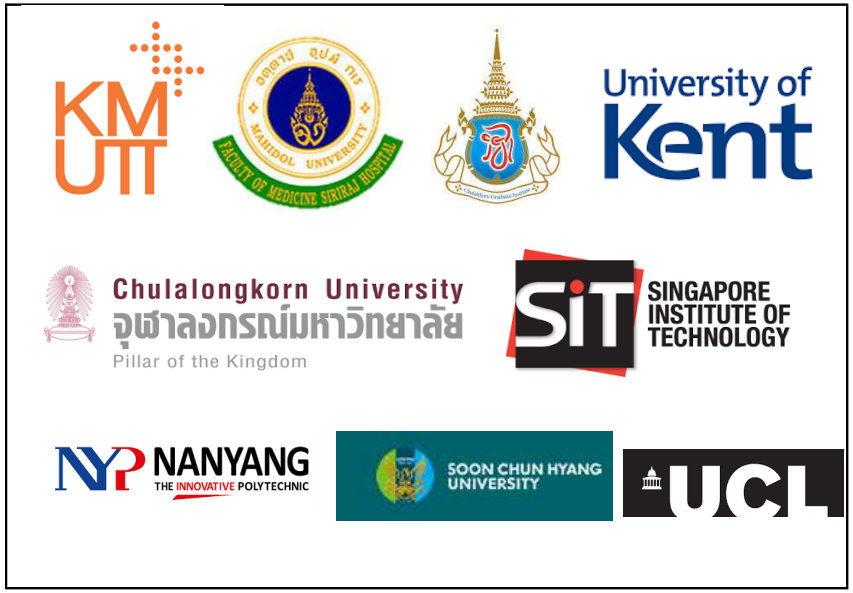
TCELS
Thailand Center of Excellence for Life Sciences

- Trastuzumab biosimilar
  - Treatment of HER2+ breast cancer
- Thailand's first locally developed mAbs biosimilar
- Chulabhorn Research Institute
- Impacts:
  - 12,000 patients per year
  - 47,000 per dose (approx. 1 million Baht/patient)
- Status
  - MOU signed, clinical trials by 2022
  - 3 successful pilot-scale batches

KinGen Biotech/NBF's ecosystem

PHARMACEUTICAL COMPANIES

ACADEMIA



GOVERNMENT AGENCIES

Highlight 2021

- EPO
  - BioSidus' HEMAX (Tech transfer, commercial project)
- HPV program
  - Genexine's therapeutic HPV vaccine for treatment of later stage cervical cancer (Phase I/II)
- Covid-19 vaccines
  - BAIYA Phytopharm
    - rProtein purification (Phase I,II)
  - Bionet-Asia
    - pDNA (Covigen, Phase III - commercial)
  - NSTDA
    - Ad5 (Phase I/II)
- Expansion
  - Unit 3: Pre-filled syringes
  - Unit 4: Cell culture (2,000 L)


Thank you!
Contact: panit.k@kingenbiotech.com