

Opportunities for process intensification and waste management

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We make difficult choices,
but we never compromise
Quality, Compliance or Safety.

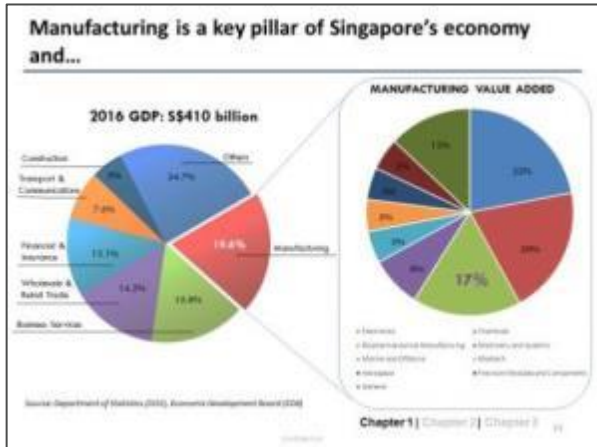
Small Molecule API Adds Significant Value in Singapore

29 Manufacturing Plants

*20 Small Molecule Plants

- ❑ VA per employee: (\$1.7 mil)
- ❑ VA: \$11.775b
- ❑ S\$18B output
- ❑ 6,914 employees

*Source: 2016 Economic Survey of Singapore
(Both Biologics & Small Molecule)





Breakthroughs that change patients' lives®

<https://www.pfizer.com/>



Inflammation
& Immunology



Internal Medicine



Oncology



Rare Disease



Vaccines



Biosimilars

Our Products

Source: Pfizer 2018 Annual Review

125

MARKETS
in which Pfizer sells
products

58

MANUFACTURING
sites worldwide

MORE THAN
92,400

COLLEAGUES
around the world

\$53.6

BILLION
in actual revenue (2018)

Global Established Pharma



CELEBREX
(CELECOXIB CAPSULES) 100 mg
200 mg

IV/Oral
ZYVOX
(linezolid)

Depo-Provera
Contraceptive Injection
medroxyprogesterone acetate injectable suspension

LYRICA
PREGABALIN

VIAGRA
(sildenafil citrate) tablets

Global Innovative Pharma

Eliquis
(apixaban) tablets



CHANTIX
(varenicline) TABLETS
It's all about getting there.

Genotropin
(somatropin [rDNA origin] for injection)

Enbrel
etanercept

Vaccines, Oncology and Consumer Healthcare

Prevenar 13
polysaccharidevaccin mot pneumokockinfektioner, konjugerat, adsorberat, 13-valent

Trumenba
Meningococcal Group B Vaccine

XALKORI
CRIZOTINIB
250 MG CAPSULES

SUTENT
sunitinib malate
capsules

Centrum
ADVANCED FORMULA

ChapStick

Pfizer Asia Pacific Pte Ltd (PAPPL)

Tuas, Singapore



Singapore's multi purpose organic synthesis plant (PAPPL) is where 5 of Pfizer's top 10 drugs-by-revenue are made

Lyrica – US\$ 4,969 M

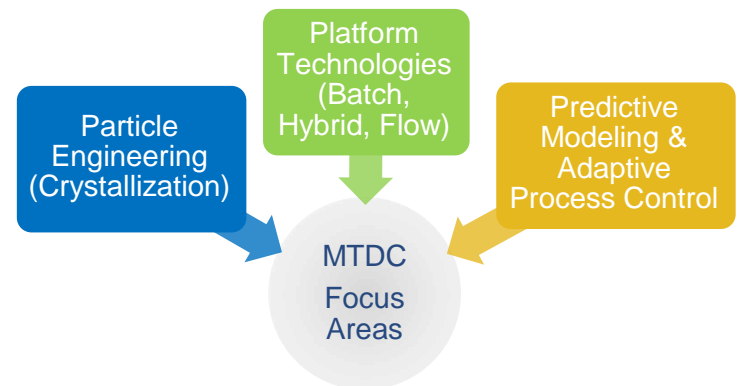
Ibrance – US\$ 4,188 M

Xeljanz – US\$ 1,774 M

Sutent – US\$ 1,049 M

Norvasc – US\$ 1,024 M

Manufacturing Technology
Development Centre (MTDC)



Pfizer Global support on financing energy efficient investments

Pfizer is integrating environmental sustainability into business operations through our Green Journey.

- 
- ❖ Energy Efficiency
 - ❖ Green Building
 - ❖ Green Chemistry
 - ❖ Green Design
 - ❖ Greening Our Fleet
 - ❖ Renewable Energy
 - ❖ Packaging
 - ❖ Waste & Recycling
 - ❖ Water Use

Pfizer's Environmental Sustainability Goals

Compared with a 2012 baseline, by the end of 2020 Pfizer will:

- Reduce greenhouse gas emissions by 20%
- Reduce the amount of waste disposed by 15%
- Reduce water withdrawal by 5% (excluding non-contact cooling water)

Raising the Bar with Technology

Moving from API Manufacturing Processes involving consecutive stages of readily reproducible, traditional batch chemistry to Bespoke sequence of manufacturing process stages using proprietary technology, not easily accessed by conventional producers

Batch manufacturing



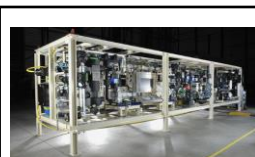
Standard Lab



Traditional Batch Plant

- Synthetic Organic Chemists
- Chemical engineers

Continuous Manufacturing



Continuous Stage



Advanced Process Control



Digitalisation IIOT



Biocatalysis



Decontamination Platform



Hybrid Plant

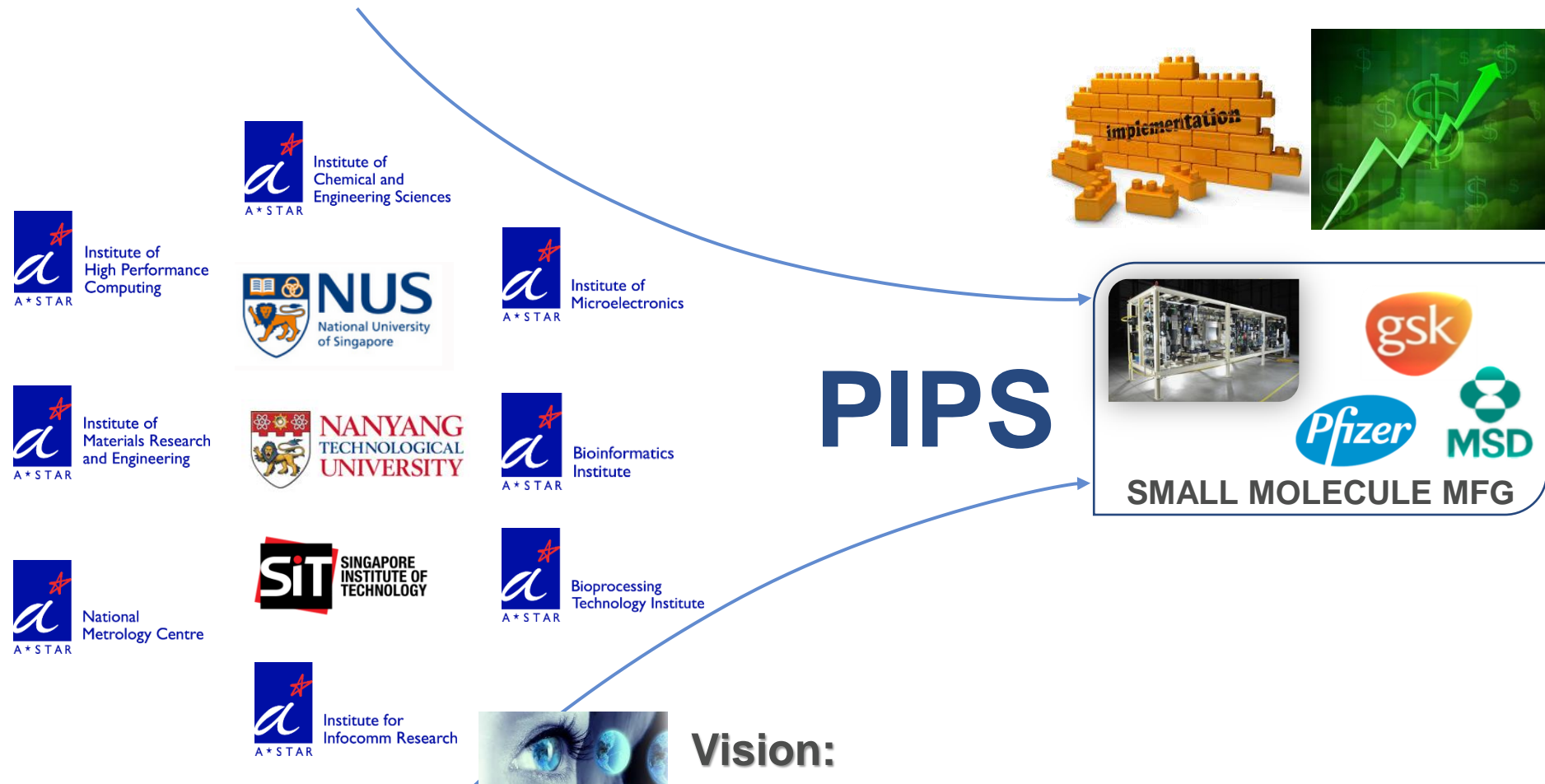
New Capabilities Required

- Computational Modelling & Design
- Kinetics/Flow Engineers
- Advanced Process Control/ Machine Learning
- Robotics / Augmented Reality
- Process Analytics
- Data & Systems Integrators
- Data Integrity
- Encryption & Cyber Security

- Synthetic Organic Chemists
- Chemical engineers

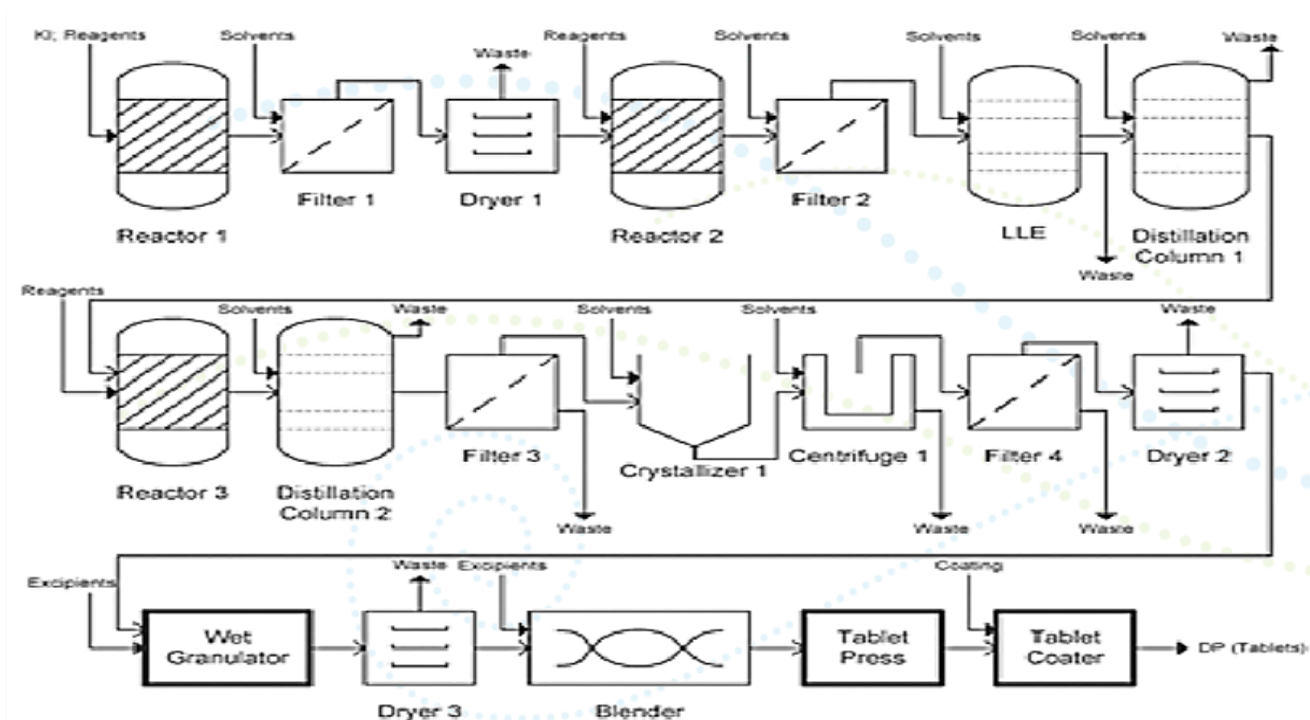
Pharma Innovation Programme Singapore (PIPS)

Translating ideas into value...



Lead the global transformation of Pharma Manufacturing to create unique value for Patients, Pharma and Singapore...

Synthesis of active pharmaceutical ingredients (APIs)



Separation processes (i.e. distillations, filtration, centrifugation) make up 40-70 % of capital and operating costs¹.

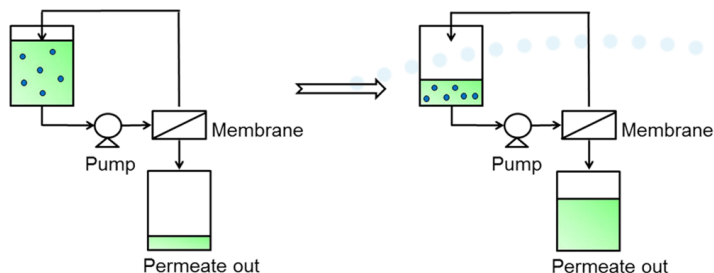
Where might we usefully apply membranes for API manufacturing?

2 broad potential areas

1. Process intensification

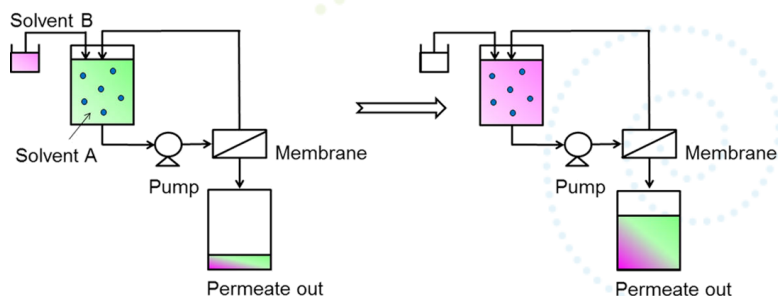
(a) Concentration

Defining feature: at least one solute and one solvent



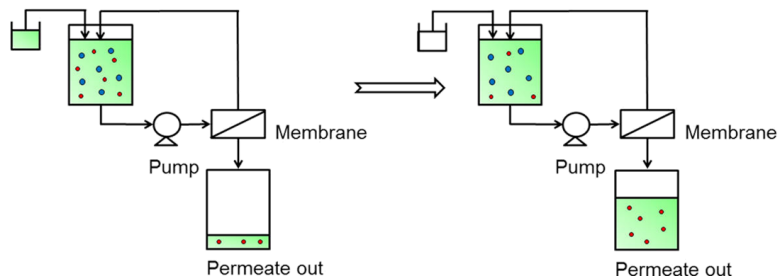
(b) Solvent exchange

Defining feature: at least one solute and two solvents



(c) Purification

Defining feature: at least two solutes and one solvent



Processes

- Concentration of API/intermediate
- Solvent exchange
- Purification
removal of impurities/byproducts
from products [<900 Da]
- Cooling
- Dilution
- Reaction/bio-reactions
- Crystallisation

Comparison with current operations



Operation	Solvent Swap	Water removal	
Initial stream composition	Toluene/THF mixture with IPA and API	Ethyl acetate (97.1%), water (2.9%), traces of methylene chloride plus API	MTBE (~98.5%), water (~1.5%) and API
Typical process	4 distillations	2 vacuum distillation	Dean Stark Reflux
Volume/ Time	6600 L/ 60h	6400L/ 10-30h	6700L/ 12h, < 25 °C
Stream specifications	IPA with product spec of < 1 wt.% THF and <1 wt.% toluene;	Ethyl acetate stream with < 0.6 wt% water	MTBE stream with <0.2 wt% water

2. Waste management ^a

Eliminating environmental contamination from water released to public sewers and reduction for **waste incineration**.

Challenges:

- traces of API, metals and organic solvent
- halogenated waste (incl. chlorinated aromatics)

Cost of incineration ~\$ **millions** globally per annum



Moving from paper to plant

Checklist for implementation

- Organic solvent compatibility
(THF, DMSO, MTBE, DMF etc)
- Stability (no leechables)
- Reasonable resources and timelines for commercial vs specific solution development
- Proof-of-Concept at scale
- Value calculations



Benefits

- ✓ Improved separation efficiency
- ✓ lowered cycle time and costs,
- ✓ environmental sustainability, and
- ✓ continuous operations

Summary

- Waste management and process intensification are two broad interest areas.
- Development of talent pool and advisors for translation and implementation of membranes at industrial scale will be valuable.
- A win-win for consumers and companies with increased productivity, continuous improvement, lowered costs, and reduced environmental impact.



Thank You!

For queries and opportunities,
kindly email David at
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