Bioprocessing Technology Institute
BTI

Biologics Pharma Innovation Programme Singapore (BioPIPS)

Grant Call for (1) Sensing and Modelling and (2) Sustainability

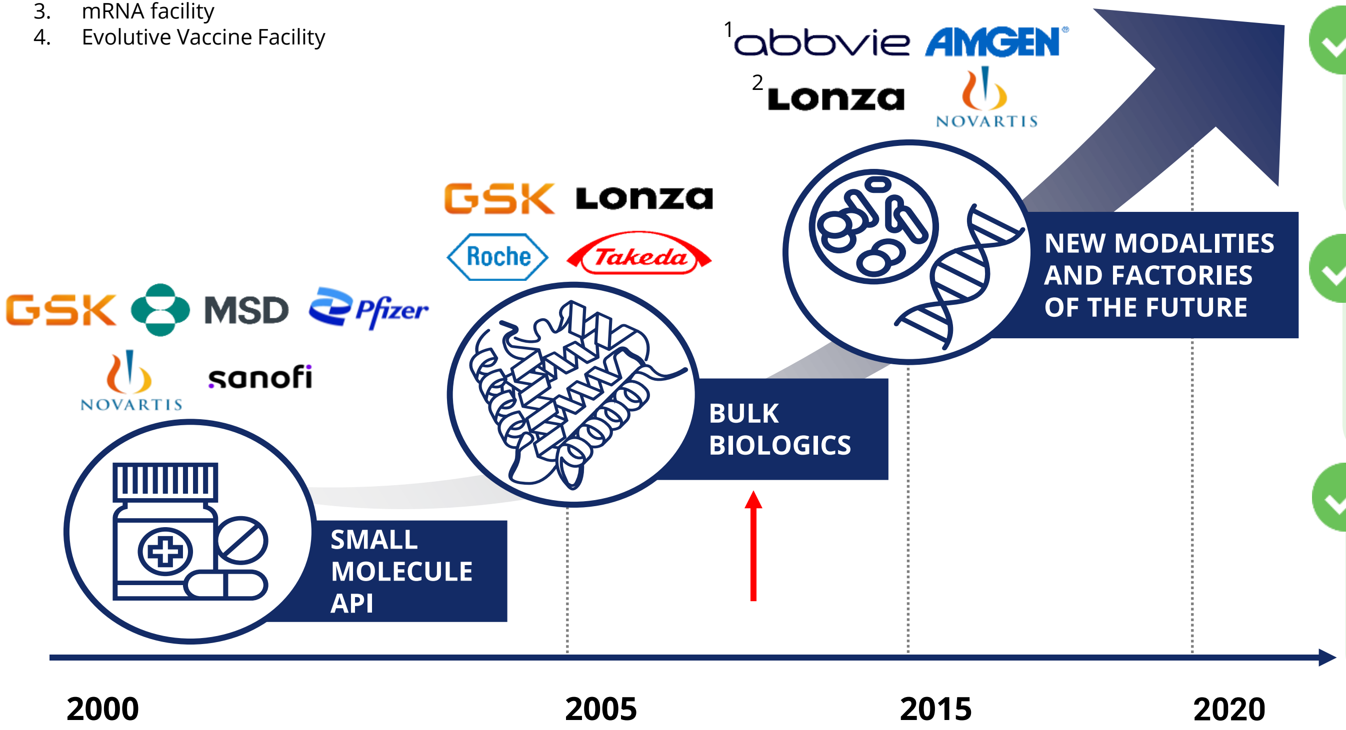
Content

CREATING GROWTH, ENHANCING LIVES

Pharmaceutical Manufacturing in Singapore

> 30 plants across diverse modalities

1. Cell therapy CDMO (Contract Development and Manufacturing Organisation)
2. First-of-its-kind SUT (Single Use Technology) facility globally
3. mRNA facility
4. Evolutive Vaccine Facility



2020 BIOPHARMA SECTOR PERFORMANCE

Manufacturing Output
S$15.7B

Value Added
S$8.8B

Employment
>8,900 employees

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Multi-Pronged Strategy

Helping companies meet new needs and enhancing Singapore's competitiveness

Technology

Driving productivity, encouraging introduction of new products and enabling manufacturing of new modalities

Strengthening existing manufacturing base via process and technology innovations

Preposition Singapore for manufacturing of new therapeutic modalities

Manpower

Growing and strengthening our base of manufacturing talent

Preparing an industry-ready workforce

Equipping workers with the right skills through local and overseas on-the-job training

Enabling workers to build a career across various levels of experience

Infrastructure

Providing industry with innovative capacity solutions

Increasing outsourced development and manufacturing capacity in Singapore

Providing flexible infrastructure options

Supplier Ecosystem

Diversifying the supplier and supply chain ecosystem

Identifying critical supply gaps in the supplier ecosystem

Encouraging new suppliers who can meet these needs to set up in Singapore

Sustainability

Supporting sustainable growth and operations in Singapore

CO_2

Advancing decarbonisation pathways for industry

Expanding capabilities in circular economy

Growing an enabling environment to support sustainability needs

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Technology Innovation and Development

Accelerating manufacturing technology development and implementation in Singapore sites

Biopharmaceutical Deep Dive endorsed by MTC EXCO on 7 September 2022

LEVERAGING ADVANCED MANUFACTURING TECHNOLOGIES

Strengthen the Existing Manufacturing Base through Process Innovations

Preposition Singapore for Manufacturing of New Therapeutic Modalities

SMALL MOLECULES

Pharma Innovation Programme Singapore (PIPS)

Active Ingredient to Product Interface

Agile Factory of the Future

Manufacturing Technology Platforms

Plant Operations

Tools for Accelerated Process Development and Process Technologies

GSK MSD Pfizer syngenta

BIOLOGICS

Biologics Pharma Innovation Programme Singapore (BioPIPS)

Sensing and Modelling

Sustainability

Compliant Agility

BIONTECH GSK sanofi

CELL THERAPY

Singapore Cell Therapy Advanced Manufacturing Programme (STAMP)

Autologous T-cell Therapy Manufacturing

Mesenchymal Stem Cell Manufacturing

Critical Analytics for Manufacturing Personalised Medicine Programme

GENE THERAPY

Nucleic Acid Therapeutics Initiative (NATi)

Smarter Drug Design

Process Optimisation

Targeted Delivery

NATi

About BioPIPS

Objectives

Leverage public sector R&D capabilities to –

- ***Address problem statements*** from local biologics manufacturing facilities
- ***Enhance manufacturing productivity and operational efficiency***

Desired Outcomes

Transform the existing biologics manufacturing operations in Singapore so that the manufacturing sites are –

- ***Best-in-class*** within their respective manufacturing network
- Well positioned for the ***introduction of new products and novel manufacturing technologies***

Case for BioPIPS

Leverage strong foundation to launch BioPIPS

- ***Synergies*** in operations, resources, learning and collaboration of technologies with PIPS
- ***Interest*** from companies to form the consortium

Definition of Workstreams through Industry Roundtable Discussions

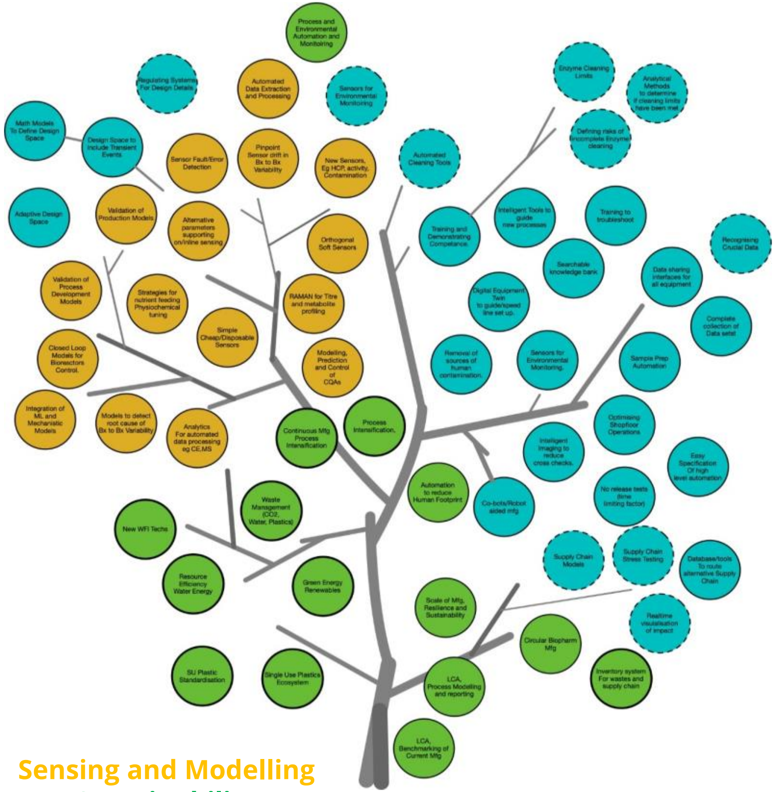
BIONTECH GSK sanofi

These workstreams are generated through discussion to address the dual challenge of (1) Directing research to improve productivity of existing manufacturing capabilities and (2) Exploring solutions to fundamentally improve the long-term resilience and sustainability of vaccines and biopharmaceuticals manufacture.

Sensing and Modelling – focuses on generating fast, in-process and automated workflows to translate process performance into actionable knowledge. Specifically, the aim is to improve the accuracy and robustness of sensing technologies and facilitate the incorporation of AI and modelling approaches into manufacturing processes to enable quicker and more effective product and process control.

Sustainability – focuses on technologies to achieve sustainability targets. These include using models to identify bottlenecks in manufacturing and supply chain, exploring impact of new technologies to reduce resource utilisation and re-thinking the expanded utility of single-use equipment through the lens of materials science and circular economy considerations.

Compliant Agility – focuses on removing manual tasks to achieve greater productivity in the manufacturing facilities while maintaining compliance status by using solutions, e.g. robotics and advanced analytics.



Sensing and Modelling
Sustainability
Compliant Agility

Sensing and Modelling

Sensing and Modelling

Batches of biopharmaceuticals are expensive with tight manufacturing regulations. Current manufacturing processes **follow exact recipes** to **control quality and yield of products**. The ability to control biological processes is constrained by the capability to monitor, analyse and combine data to gain insight.

In the **Sensing and Modelling** workstream, the aim is to develop and validate in-process, automated analytical workflows to ensure **accurate monitoring** of **process parameters and product quality** which will in turn **facilitate adaptive control strategies** in the form of real- or near real-time corrections to manufacturing unit operations. These objectives will be achieved through **improvement of sensor technologies** and the **incorporation of modelling techniques** to predict outcomes and enact changes to manufacturing conditions.

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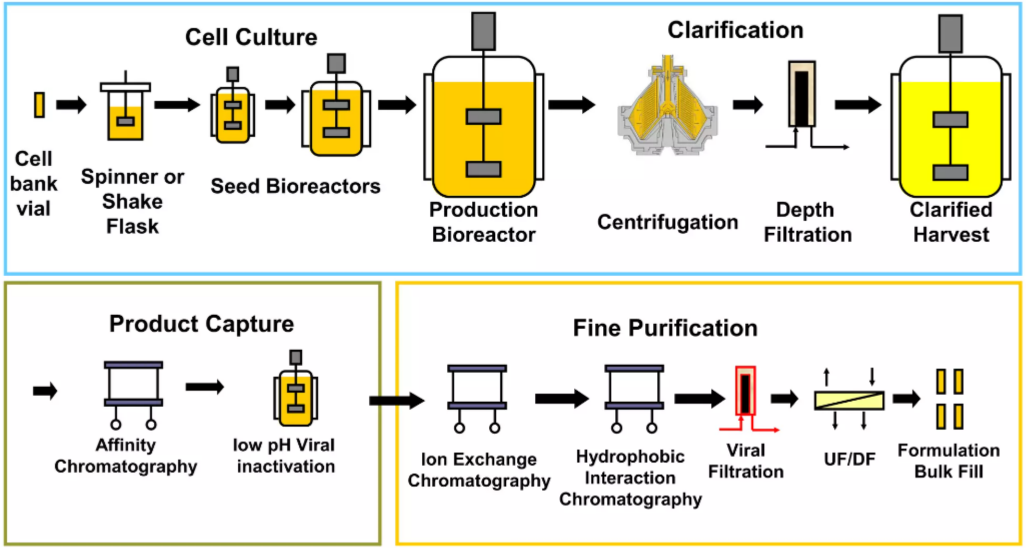
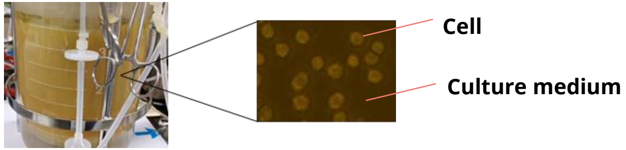
Typical Equipment Train for Biologics and Vaccines Manufacture

Image from Worcester Polytechnic Institute



Images from Samsung Biologics

Bioreactor cell culture



Images from Bioprocessing Technology Institute, A*STAR

Image from Sartorius

Real-time Monitoring of Process Parameters and/or Product Titre using Raman Spectroscopy in Multiple Scales

Problem Statement 1 – Development of Experimental Space to Generate Data of Interest from Bioreactors

Scope

- In at least 2 scales with industry input, build model bioreactor systems, and formulate standard Raman spectroscopy methodologies and complementary offline measurements methods
- Collect time series data to form current state-of-the-art benchmark source data sets
- Define data standards and format using data repository platforms and signal processing technologies
- Store the data in a defined database for public access

Problem Statement 2 – Processing of Signals from Raw Data

Scope

- Develop computational techniques to filter noise from Raman signals to generate clean peaks/patterns
- Write software to automatically identify peak signals corresponding to parameters/attributes of interest
- Set up approaches to identify important signals accurately and monitor proper operation of Raman spectroscopy sensors, including inventing technologies to detect faults in the sensors via its peak signals
- Invent novel approaches to track specific peaks of interest over time while accounting for signal drift in different scales

Real-time Monitoring of Process Parameters and/or Product Titre using Raman Spectroscopy in Multiple Scales

Problem Statement 3 – Development of Multivariate Prediction Models for Parameters/Attributes of Interest

Scope

- Develop advanced machine learning/artificial intelligence algorithms for feature selection and mapping of Raman spectroscopy spectra in regression prediction tasks, e.g. glucose concentration in a bioreactor
- Explore how models interpret signals over multiple scales and time to predict parameters/attributes of interest across each scale
- Using the models or otherwise, identity the factors causing scale up issues
- Explore hybrid algorithms to explain observed phenomena

Problem Statement 4 – Investigating Physical and Biological Principles Behind Scale Up Changes

Scope

- Develop framework and methodologies to provide mechanistic understanding of scale up issues
- Investigate and understand physical and biological changes over time at different bioreactor scales

Desired Outcome

Demonstration of a model to monitor a variable of media/product quality in a small bioreactor scale with the same model ported to monitor the same variable at a larger scale

Real-time Monitoring of Process Parameters and/or Product Titre using Raman Spectroscopy in Multiple Scales

Note: Problem Statements 1 – 4 are integrated. PIs are encouraged to form multidisciplinary teams to address the problem statements. A key part is to integrate the output of the projects (refer to diagram below) to meaningfully create multi-scalable models which can be used for adaptive control in the future.

Problem Statement 1 –
Development of Experimental Space to Generate Data of Interest from Bioreactors

Problem Statement 2 –
Processing of Signals from Raw Data

Problem Statement 3 –
Development of Multivariate Prediction Models for Parameters/Attributes of Interest

Problem Statement 4 –
Investigating Physical and Biological Principles Behind Scale Up Changes

Real-time Monitoring of Process Parameters and/or Product Titre using Raman Spectroscopy in Multiple Scales

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Applicant Requirements

1. Wet Laboratory
   a. Mammalian cell culture growth in commercial media to secrete antibody proteins
   b. Perform cell cultures at a minimum of 2 bioreactor scales, e.g. 5 L, 50 L
   c. Measure offline critical process parameters (CPPs) and/or critical quality attributes (CQAs)

2. Advanced Computational Techniques
   a. Ability to perform advanced computational techniques to process Raman spectroscopy spectra (RS), including techniques to remove noise, visualise data, correct baseline, pick and quantify peak signals
   b. Ability to develop advanced machine learning (ML) algorithms for feature selection, map RS between 2 different bioreactor sizes, regression prediction, e.g. glucose concentration in a bioreactor
   c. Ability to design and develop databases
   d. Ability to leverage physics and biology to provide mechanistic insight into how probe interference can be reduced as the culture environment changes continuously when cells grow and protein titre correspondingly increases
   e. Combine mechanistic understanding with ML through hybrid approaches to improve measurement of CPPs/CQAs

Real-time Monitoring of Process Parameters and/or Product Titre using Raman Spectroscopy in Multiple Scales

Recommended Timeline

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Current Grant Call												
Problem Statement 1 – Development of Experimental Space to Generate Data of Interest from Bioreactors												
Problem Statement 2 – Processing of Signals from Raw Data												
Problem Statement 3 – Development of Multivariate Prediction Models for Parameters/Attributes of Interest												
Problem Statement 4 – Investigating Physical and Biological Principles Behind Scale Up Changes												
Wave 2 Grant Call, e.g. Process Control												
New Problem Statements												

Sustainability

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Sustainability

Biopharmaceutical and vaccine manufacture faces 2 key sustainability challenges – (1) Exploring resilient and sustainable supply chains and biomanufacturing facilities and (2) Evolution of Single Use Technology (SUT) and equipment.

In the **Sustainability** workstream, the starting point is a macro level view on what a **sustainable ecosystem for manufacture** constitutes, i.e. relationship between suppliers of raw materials/components, biomanufacturing operations to promote sustainability, optimisation of resource (energy, water) utilisation, productivity and waste management.

The 2nd strand is a fresh look at **SUT** and equipment through the lens of materials science while considering circular economy factors.

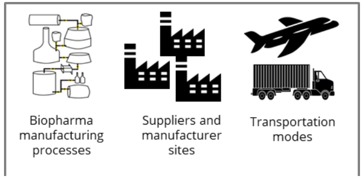
<u>Common sustainability goals</u>

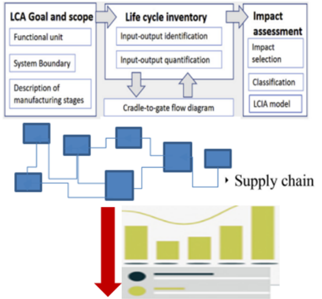
Limit environmental footprint

Sustainable sourcing and circular economic solutions

Zero waste-to-landfill

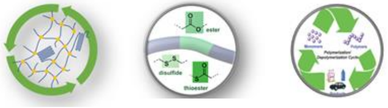
Reduce GHG and carbon emissions





Main Indicator	Performance Metrics
Net CO_2 emission	Net CO_2 emission via LCA from "Cradle-to-Gate"
Revenue-Costs	Profit making potential
Technological feasibility	Potential scale of processes, efficiencies and product yields
Feedstock	Types, locations, sources, quantities
Supply security	Logistics, supply chain inventory management

Materials Innovation



Vitrimers

Chemo-Degradable Plastics

Close-the-Loop Polymers

Single Use Technology and Equipment in Biopharmaceutical Manufacturing

Image from Sigma Aldrich

Image from CelBios

Image from Entegris

Image from Sanisure

Image from Cell Culture Dish

Image from Lubrizol

Image from Sartorius

Image from International Society for Pharmaceutical Engineering (ISPE)

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Technologies for Single Use Plastics Downcycling/ Recycling/Upcycling

Problem Statement – Technologies to Downcycle/Recycle/Upcycle Single Use Plastics

Single use plastics have been utilised in biopharmaceutical manufacturing for bioreactor cell cultivation, product purification, buffer preparation, holding tanks, fluid transfer, packaging, filters, etc. Plastic materials from manufacturers are often different, hence there is limitation for downcycling, recycling and upcycling of such wastes. Plastic downcycling/recycling/upcycling is seldom performed in biopharmaceutical manufacturing because – (1) Plastic wastes are typically mixed, (2) Proprietary IP of some plastics prohibit transfer out of the manufacturing facility and (3) Plastic wastes have contacted biohazard materials. As such, plastic waste is typically incinerated.

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Technologies for Single Use Plastics Downcycling/ Recycling/Upcycling

<u>Scope</u>

- Development of plastic downcycling/recycling/upcycling technologies to enable implementation in biopharmaceutical manufacturing facilities to fulfill zero waste-to-landfill goal, including analysis to describe process economics, resource use and GHG emissions
    - Plastic waste characterisation to enable recycling, e.g. plastic composition analysis, mixed waste characterisation, fast moisture analysis
    - Automated plastic sterilisation, shredding and sorting, e.g. gravimetric sorting, spectrometry-based sorting
    - Technologies to separate and/or recycle mixed plastic wastes, e.g. pyrolysis, biochemical treatment, supercritical fluid extraction
    - Technologies to increase value of plastic waste while incorporating sustainability considerations, such as CO_2 emissions, energy and water use
    - Clean room/GMP factory design for segregated plastic waste collection
    - Alternative environmentally friendly solutions to single use plastics

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Technologies for Single Use Plastics Downcycling/ Recycling/Upcycling

Scope

- Develop novel materials to replace single use plastics
    - Innovate layered materials more amenable for recycling
    - Invent new sustainable materials to replace single use plastics

Desired Outcome

- Enable downcycling/recycling/upcycling of plastic wastes from biomanufacturing facilities to reduce waste-to-landfill, GHG and carbon emissions
- Cost effective and sustainable solutions for plastic recycling/upcycling for commercialisation

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Administrative Notes

Eligibility

1. The Principal Investigator and Co-Investigators as defined in Grant Terms and Conditions must:
    a. Hold a primary appointment in a Singapore publicly funded research institution or an Institute of Higher Learning. The Principal Investigator must hold a primary appointment of at least 0.7 FTE in Singapore.
    b. Lead a laboratory or research programme which carries out research in Singapore
    c. Possess track record of leadership ability in coordinating research programmes and providing mentorship to research teams as well as having productive research outcomes. A track record in securing IRS will be advantageous.

2. Collaborators as defined in Grant Terms and Conditions are not eligible to receive funding
    a. Companies can participate in projects only as collaborators

3. Exceptions to the above eligibility criteria will be considered on a case-by-case basis. Please submit a request to the BioPIPS Programme Office at least 7 days before the closing date of the grant call.

Important Notes

1. Applicants must use the latest version of the Letter of Intent (LOI)/proposal template
2. Submissions should clearly state milestones and deliverables. Industry collaborations are strongly encouraged.
3. Applicants shall comply with grant terms and conditions, including prevailing regulations

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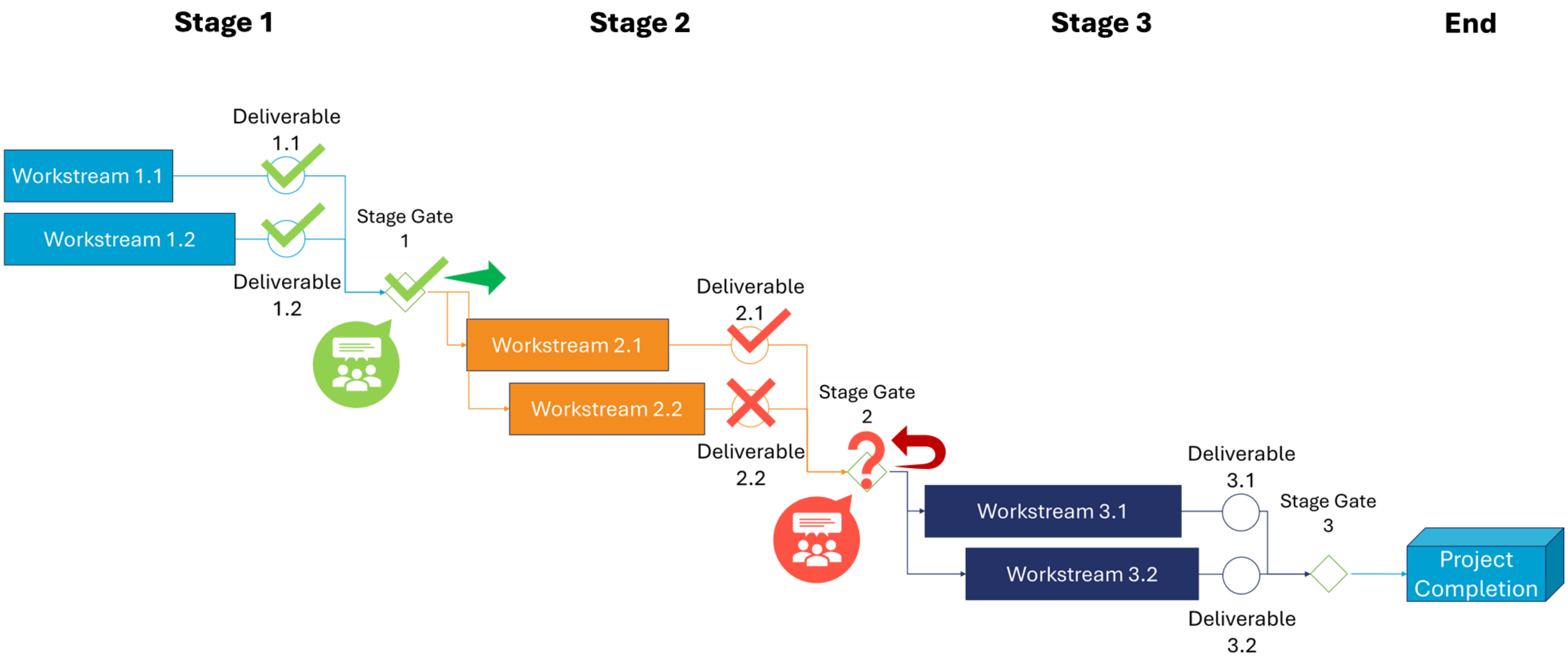
Example of Stage-Gated Project Management



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Evaluation Criteria

1. Relevance to Problem Statement(s)
2. Potential for commercial adoption
3. Scientific quality and innovativeness
4. Experience and expertise of the team
5. Effectiveness of project management
6. Appropriateness of the requested budget
7. Strength of intellectual property (IP) strategy
8. International competitiveness

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Contact Us

For all enquiries, contact the BioPIPS Programme Office at –

biopips@bti.a-star.edu.sg

BioPIPS website address –

https://www.a-star.edu.sg/bti/programmes-in-bti/biologics-pharma-innovation-programme-singapore-(biopips)

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THANK YOU

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