Total Solutions

for cGMP manufacturing of viral vectors

TFBS Bioscience, Inc.

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1. Company Overview

1.1 About Us

TFBS Bioscience Inc. is the leading GMP viral vector contract development and manufacturing organization in the Asia-Pacific region and the first viral vector manufacturing provider in Taiwan.

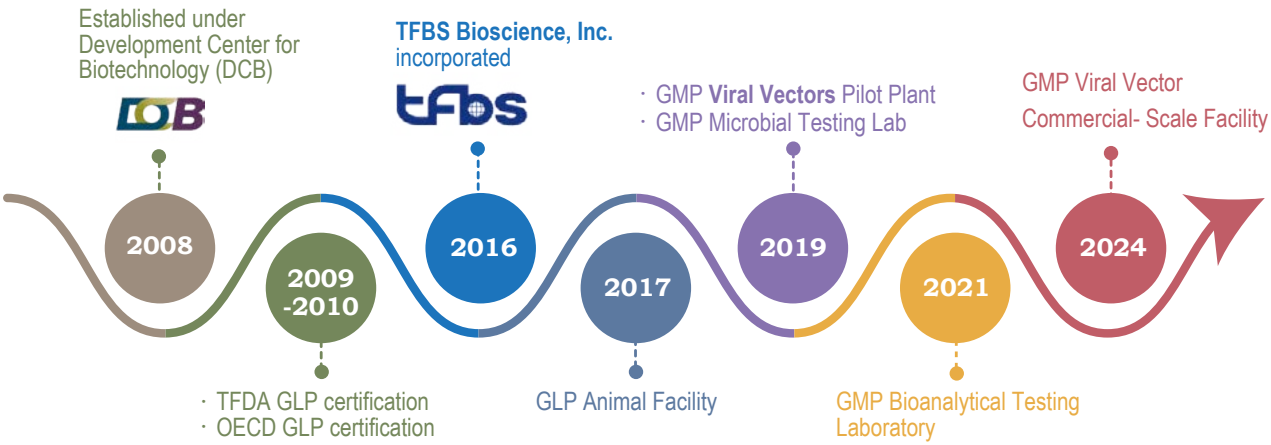
With the expertise in manufacturing and comprehensive testing services, we always stand by our clients and help them meet their needs through continuous communication.

We are proud to offer total solution services with flexible scheduling that consistently supports our clients to get their products into the market as quickly as possible.

1.2 Our History

TFBS was founded in 2016 as the first Contract Research Organization (CRO) focusing on biosafety and quality testing in Taiwan. However, our executive team's roots run deeper, going back to the virus research laboratory founded in the Development Center of Biotechnology (DCB), a leading life science research institute sponsored by government in Taiwan. With over a decade of experience, TFBS has provided cost-effective and validated testing services to biopharmaceutical companies in Asia.

In 2019, we have expanded our services to GMP-compliant viral vector manufacturing at our pilot facility. With our expertise in viral vector manufacturing and advanced equipment in the state-of-art facility, we are pioneering entrepreneurship to become a partner for the gene and cell therapy community.



TFBS commerciall-scale manufacturing

- 53,000 sq ft
- Cell and virus banking
- LV, AdV, AAV, and RV
- Suspension and adherent cell manufacturing systems
- Process development
- 4 manufacturing lines
- Aseptic fill & finish
- QC release

1.3 Our Services

TFBS provides two main services: one service is the viral vector manufacturing for cell and gene therapy products. With established expertise and effective communication, TFBS has successfully completed several customized viral vector manufacturing projects. Another service is to provide biosafety testing and product release testing for cell and gene therapy product, vaccines and biologic product. Based on over a decade of experience rooted back in the development stage associated with the government research institute, TFBS also acquired expertise to support clients in assay development and optimization for their product development.

CDMO

- AAV Manufacturing
- Lentivirus Manufacturing
- Adenovirus Manufacturing
- Retrovirus Manufacturing
- Cell and Virus Banking

CRO

- Preclinical Animal Safety Testing
- Cell Bank and Virus Seed Characterization
- Viral Clearance
- Bulk Lot Release Testing
- Preclinical and Clinical Samples Analysis
- Customized Assay Development and Analysis for Preclinical/Clinical Samples

Viral vector manufacturing

TFBS provides viral vector manufacturing for various types of viruses, including Adeno-Associated Virus (AAV), Lentivirus (LV), Adenovirus (Adv), Retrovirus (RV), and customized vector for the use in research/preclinical or clinical studies (GMP-compliant, up to phase II).

Moreover, in response to clients' commercial demands in cell and gene therapy products, TFBS has initiated the construction plan of a GMP-grade manufacturing facility for viral vectors, scheduled to be completed in 2024.

Your Best Solution Provider

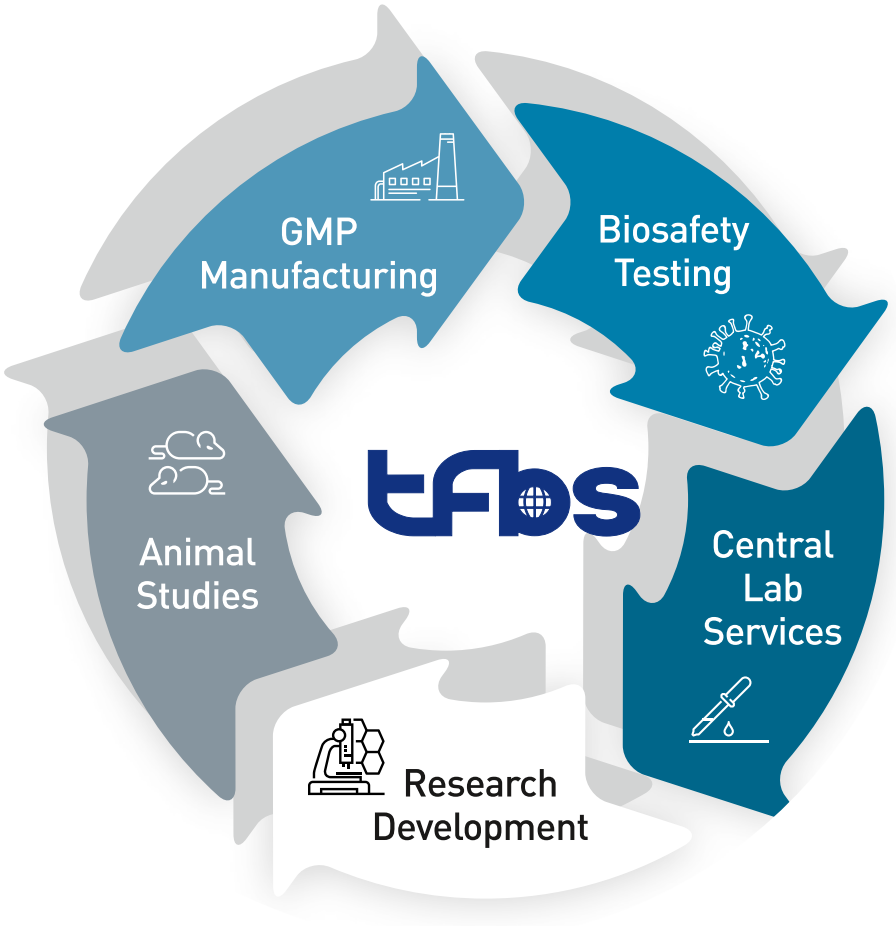
- **Diversity of viral vectors**
- **Flexibility in customer-care**
- **Scalability of production**
- **One-stop-shop service**
- **Problem solving provider**

Testing

TFBS has abundant experiences in a wide array of GMP/GLP biosafety testing services, including cell bank characterization, viral clearance, bulk and lot release testing, assay development in vitro and in vivo, clinical sample analysis, and cleaning validation for reusable medical devices.

Our dedicated scientists are able to perform method development, transfer, optimization and validation of customized assays with high quality. We have track records in meeting the requirements of regulatory authorities worldwide, such as International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), European Pharmacopoeia (EP), and United States Pharmacopeia (USP). TFBS is in full compliance with Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) standards.

Finally, TFBS offers a One-Stop-Shop service to provide comprehensive QC testing for viral vectors and related biological safety testing services. Our cost-effective approach will prove that we are your reliable partner for product development.




2. TFBS Manufacturing Technologies and Platforms

2.1 What are Viral Vectors?

How do viruses work?

Viruses attack hosts and transfer their genetic code, which contains instructions on how to make more copies of virus, into the host cell and reprogram the cell to replicate their viral genome. The host cell will then carry out these instructions to produce copies of the virus, infecting an increasing number of cells. Some viruses will physically insert their genes into the host's genome, thus incorporating the genetic materials of that virus into the genes of host cell for stable expression of viral proteins.

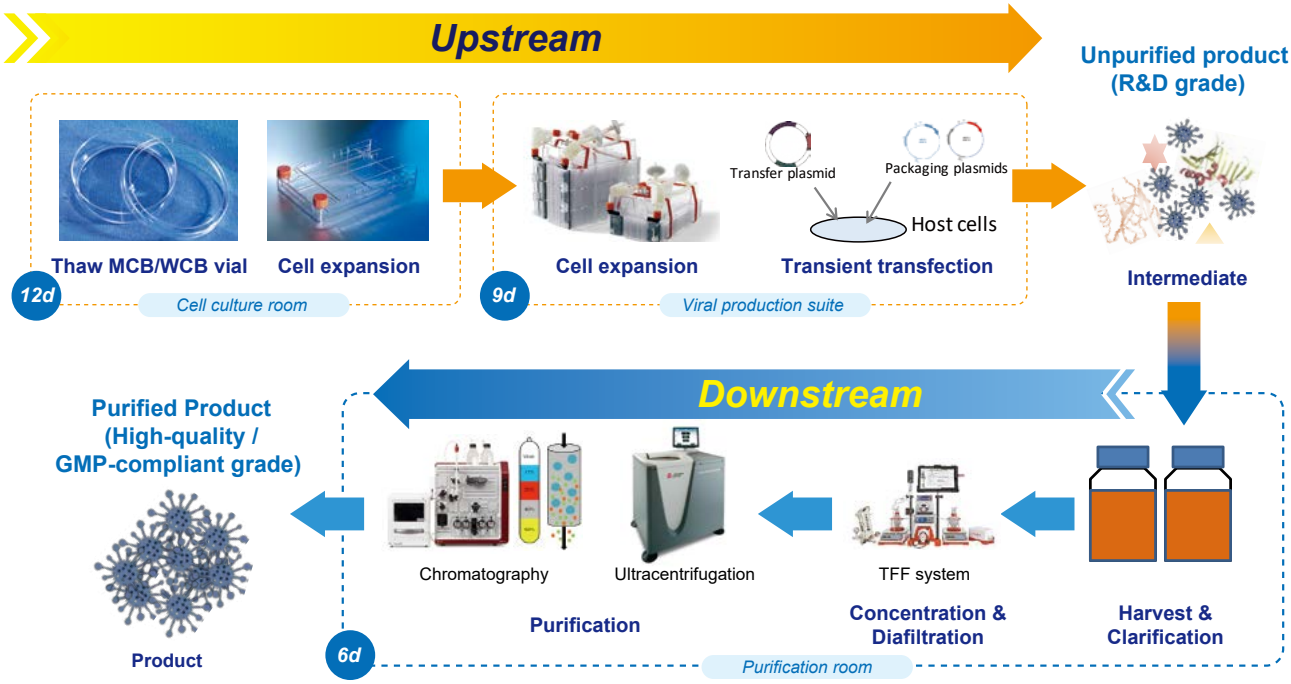
How are viruses used in gene therapy?

These types of viruses can be used as vectors, vehicles designed to deliver "desired" genetic materials directly into human cell. The viral vector technology has long been extensively studied, researched, and is determined to be safe for use in humans.

In response to the broad demand in the market, TFBS provides manufacturing services for adeno-associated virus (AAV), lentivirus (LV) and retrovirus (RV) for different development stages, from research, pre-clinical studies to clinical studies (GMP-compliant, maximum capacity of up to phase II) in our pilot facility. With the customized manufacturing process along with comprehensive QC testing, TFBS offers one-stop services with flexible timeslots to meet your timeline, a competitive price to meet your budget, and a customized service to achieve your project goal.

2.2 Manufacturing Process Overview

The TFBS experienced researchers have several years of experience in associated viral manufacturing and testing. The TFBS team has completed production projects of several different viral vectors. They always do their best to provide cost-effective solutions to meet the client satisfaction.



Vector design, construction, and production

The large amount of viral vector preparation is made possible by transfection of several plasmids into cells, including one transfer plasmid and two or more packaging plasmids. The TFBS team provides services of vector design, plasmid construction, and plasmid production to support the first step of product development. TFBS transfection platform of lentivirus and AAV has been validated by using the in-house viral vector plasmid system.

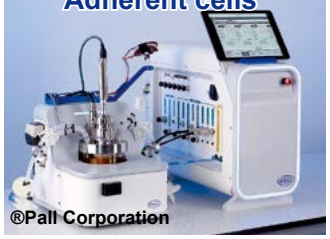
To fulfill the regulatory requirement, all cell banks used to produce plasmids need to be established in controlled areas, which should also be characterized according to regulatory guideline. TFBS is able to perform all these activities in house or with our collaboration partners.

Process development

A robust process with scalability, and later adopted in compliance with GMP regulation, is critical for the success of viral vector manufacturing. This process is achieved by a stepwise practice to improve and determine the variables involved in every production procedure based on product attributes.

The process development involves two phase: process development. The upstream phase concerns optimization of all of the procedures involved in scale-up and production of the material. The downstream phase involves optimization of procedures related to recovery, purification, and concentration of the final product. Along with process development, analytical methods also need to be developed to address product safety, potency, purity, and identity.

Expertise in Viral Vector CDMO

Upstream platforms		Downstream platforms
Adherent cells  ®Pall Corporation	HEK293T • T-flasks • Hyper flasks (multi-layer) • Cell Factory (multi-layer) • Cell stacks (multi-layer) • iCellis nano	**Ultracentrifugation** 
Suspension cells 	HEK293T • Erlenmeyer Culture Flask • Spinner flask • Wave bioreactors • Eppendorf Bioflo 320	**Chromatography** 

These processes with different scales will be developed to meet the required amount of viral vectors at different development stages. Optimization of upstream and downstream processes, performance of process scale-up, and the ability to manufacture products with desired product quality attributes are the challenges involved in GMP process development. We at TFBS have the expertise and dedication to achieve the quality requested by clients through process development. We know that each client has specific needs, and our team of virologists and engineers are committed to developing robust production and purification processes for different viruses.

The development of an efficient manufacturing process is critical to ensure that a large amount of material needed for clinical trials is produced efficiently, safely, and consistently. Beside those essence, the TFBS team is also committed to developing manufacturing procedures in a cost-effective manner for both clients and patients.

Upstream process

Our upstream manufacturing team recognizes the importance of determining optimal production conditions and can customize our workflow to meet the specific needs of any projects. TFBS have years of experience in developing upstream manufacturing processes for various serotypes of AAV, adenovirus, lentivirus, retrovirus with the capacity and the ability to manufacture virus at a variety of scales. No project is too small or too big for us.

Downstream process

For each specific viral product, the ideal conditions for cell disruption/lysis, virus isolation, and virus purification must be determined in order to obtain large amounts of material with the desired attributes of purity, and to do so with efficient use of time and resources. Our downstream manufacturing team also recognizes the importance of determining optimal purification and concentration conditions through practice of different viral vectors to meet our clients' specific needs.

State-of-the-art Manufacturing Facility

Transient transfection • 3 plasmids co-transfection system for AAV and RV • The 3rd generation plasmid system for Lentivirus	**Adherent cells** HEK293T • T-flasks • Hyper flasks (multi-layer) • Cell Factory (multi-layer) • Cell stacks (multi-layer) • iCellis nano	**Virus particle purification** • Ultracentrifugation based purification • Scalable chromatography • TFF-based purification	**Disposable technologies** • Filtration • Buffer, intermediate product, and Drug Substance preparation and storage • Container
Vector platform • Adeno-associated virus • Lentivirus • Retrovirus • Adenovirus	**Suspension cells** HEK293T • Erlenmeyer Culture Flask • Spinner flask • Wave bioreactors • Eppendorf Bioflo 320	**Chromatography** • Laboratory scale • AKTA / BioProcess system	**Tangential flow filtration** • Fully integrated TFF systemKrosFlo® KR2i, Repligen

2.3 AAV Manufacturing

Adeno-Associated Viral Vectors, or AAVs, are used to deliver small genetic material packages. They are safe and efficient for in vivo treatment. AAVs are non-integrating, meaning the genetic materials they carry are not incorporate into the cell's genome. Therefore, they are a preferred method for non-dividing target cells.

Upstream production platforms

With exclusive and customizable upstream platforms based on high producing 293T cell lines, TFBS has developed an optimized adherent/suspension culture transfection methods for AAV production (normal production >1E+14 GC/L).

Downstream purification platforms

We provide services, including iodixanol gradient ultracentrifugation and chromatography purification based on the preferences, product nature, and project development needs of our clients. Our team of specialists are experts in performing controlled processes in order to deliver products with optimal yield and purity.

AAV Production Capacity

	Research grade	High-quality grade	GMP-compliant
Production suite	  Up to **1L** in CNC [a]	  Up to **50L** in CNC [a]	  Up to **50L** in Clean room
Deliverable	Unpurified product > **1E14 GC** in total [b]	Purified product > **1E12 GC/mL** [b]	Purified product > **1E12 GC/mL** [b]
QC item	Sterility, titer	Customized	Full panel
Turnaround time	**Few days** (w/o process evelopment)	**3 months** for 50L (w/o QC testing)	**8 months** for 50L
Cost	**Please inquire**	**Please inquire**	**Please inquire**

The viral yields shown above are based on our assumption. The actual yields depend on the size of viral genome and viral vector backbone. Longer viral genome will decrease the yields.

[a] CNC: Controlled Non-Classified Area
[b] Genome copies (GC) derived from TFBS validated method

2.4 Lentivirus Manufacturing

Lentivirus can carry larger genetic material packages of RNA, which is then converted to DNA. During this process, the vectors are integrated into the genome of target cells. This makes lentivirus best suited for ex vivo treatment of dividing cells, such as T cells and stem cells. The treated cells will begin to divide and generate new cells once they are infused to the patients, and the genetic material is copied in all the newly produced cells.

The GMP-compliant production of clinical grade lentivirus for CAR-T and other gene-editing product requires knowledge of the complex methods to generate, purify, and characterize lentivirus vectors in a well-established, proven GMP quality system. As a leader of lentivirus vector production, TFBS combines the leading lentivirus production technology with comprehensive GMP procedural controls that have been developed to ensure clinical product quality, safety, and consistency for CAR-T and gene therapy products.

Lentivirus Production Capacity

	Research grade	High-quality grade	GMP-compliant
Production suite	  Up to **1L** in CNC [a]	  Up to **50L** in CNC [a]	  Up to **50L** in Clean room
Deliverable	Cultured supernatant > **1E8 TU** in total [b]	Purified product > **1E7 TU/mL** [b]	Purified product > **1E7 TU/mL** [b]
QC item	Sterility, titer	Customized	Full panel
Turnaround time	**Few days** (w/o process evelopment)	**3 months** for 50L (w/o QC testing)	**8 months** for 50L
Cost	**Please inquire**	**Please inquire**	**Please inquire**

The viral yields shown above are based on our assumption. The actual yields depend on the size of viral genome and viral vector backbone. Longer viral genome will decrease the yields.

[a] CNC: Controlled Non-Classified Area
[b] Genome copies (GC) derived from TFBS validated method

2.5 Retrovirus Manufacturing

Retrovirus are similar to Lentivirus, which inserts a copy of its RNA genome into the DNA of host cell, thus introducing changes of the host genome. The advantage that retroviral vectors offer is their ability to transform their single strand RNA genome into double strand DNA that can stably integrates into the target cell genome.

Based on expertise and experience in manufacturing and assay development, TFBS is reliable to support our clients to meet various customized demands.

2.6 Adenovirus Manufacturing

Adenoviral vectors are similar to AAV vectors, which can deliver DNA packages into non dividing cells. However, Adenoviral vectors can deliver vector genomes that are eight times the size of AAV.

With a wealth of knowledge of comprehensive methods to generate, purify, and characterize adenovirus vectors in a well-established, proven GMP quality system, TFBS provides GMP-compliant grade of adenovirus production for vaccine products.

2.7 Custom Viral Vector Manufacturing

With years of expertise and experience in various viral vector manufacturing, TFBS can be trusted to support our clients if they have needs in customization of vector production.

2.8 Cell and Virus Banking

TFBS faithfully follows GMP regulation to establish the virus/cell bank for viral vector manufacturing. The banking of master and working cell banks (MCB, WCB) is conducted in a separate, isolated, purpose-built area to ensure no cross-contamination of products can ever occur.

Through master/working bank establishment and subsequent bank characterization all in house, TFBS can assist clients to streamline the manufacturing process and accelerate the timeline for product development.

Full Panel Analytical Capability

Attributes of virus	Characteristics	Methodology
Identity	Appearance	Visual inspection
	pH	pH Meter
	Osmolality	Osmometry
	Identity	Western blot / SDS-PAGE
	Genetic composition/ integrity	NGS/DNA sequencing
Purity	Residual host cell proteins	ELISA
	Residual host cell DNA	q-PCR
	Residual DNA size	DNA gel electrophoresis
	Empty:full particles ratio (AAV)	TEM
	Residual plasmid DNA	q-PCR
	Process derived impurities	Depends
Quantity	Viral genomes titer	q-PCR
	Infectivity titer	Cell-based q-PCR
	Capsid titer	ELISA
	Transducing titer	Cell-based q-PCR
Safety	Replication-competent virus (RCV)	Cell-based assay
	Endotoxin	Kinetic Chromogent LAL assay
	Sterility	21 CFR
	Mycoplasma	21 CFR or NAT
	Adenovirus E1	q-PCR
	SV40 Large T antigen	q-PCR
	Testing for adventitious viruses	In vitro or in vivo test
Potency	Potency	Customized

3. Testing Service

3.1 Preclinical Animal Safety Testing

According to the FDA, EMA, and other regulatory guidance for pharmaceutical industry, GLP preclinical animal testing is required to address the safety issues for anticipated exposure of products in human subjects.

Pharmacology Studies - Efficacy

▶ **In Vivo Models (Rodent Species)** ● Rat ● Mouse ● Guinea pig ● Hamster

▶ **Routes of Administration**

● Intra-venous ● Intra-arterial ● Intra-cranial ● Intra-tracheal ● Subcutaneous ● Customize
● Intraperitoneal ● Intra-articular ● Intranasal ● Intracerebral ● Oral ● Intramuscular

▶ **Dosing** ● Single ● Repeated injection by 1-3 doses ● Acute
● Subchronic ● Chronic studies (14/28/90 days in general)

▶ **Disease Model**

● Respiratory (*Chronic obstructive pulmonary disease (COPD) *Rhinitis *Asthma)
● Acute liver failure (ALF) ● Inflammatory bowel disease (IBD)
● Acute/ Chronic kidney diseases (AKD/CKD) ● Diabetes
● Skin care (*Whitening ability *Humidity retention *Hair restoration)
● Cardiovascular ● Solid tumor ● Customized model

Toxicity Studies - Safety

General Toxicity Studies

- Biodistribution Study (GLP/Non-GLP)
- Genotoxicity Studies
- Local Irritability
- Tumorigenicity
- Pilot TOX Study (Non-GLP)
- Pivotal TOX Study (GLP)

Bioanalysis for Animal Testing

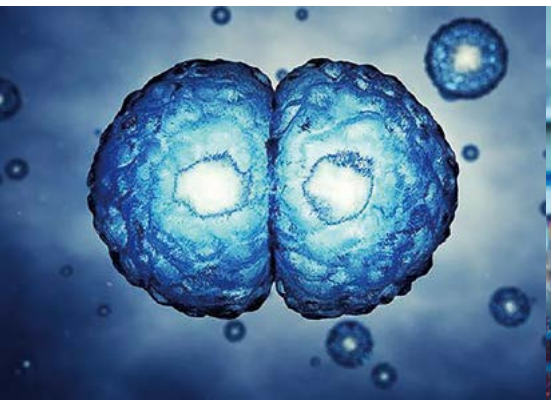
- Clinical Observation
- Histopathology (IHC, H&E)
- Cell-mediated Analysis:
  - * Primary cell culture for immunity assay
- Serum Analysis
  - * Cell-based platform
    - – Titration of neutralizing antibodies
  - * ELISA platform

3.2 Cell Bank and Virus Seed Characterization

The pivotal step to ensure the safety of biopharmaceutical product is to perform characterization and biological safety testing on the production cells or virus seeds. The objective is to confirm identity, purity, genetic stability, and tumorigenicity of these cells or viruses. Such characterization could ensure the source of cells or viruses is authentic and free from contamination of undesired cells and adventitious agents, such as bacteria, fungi, mycoplasma, mycobacteria, and virus. Generally speaking, the source of cells at different stages, such as master virus seed (MVS), master/ working cell bank (MCB/WCB), end of production cell (EOPC), unprocessed bulk, purified bulk, and final product all require different regimes of tests to ensure their safety.

TFBS works closely with our clients to develop and design cost-effective, scientifically sound, and validated testing methods for the characterization of cell and viruses. At TFBS, we offer our clients accurate, prompt, and efficient testing services for their time-sensitive projects. From preliminary testing of seed stocks to rigorous cell bank characterization, TFBS ensures that our clients can meet their requirements to comply with international regulatory guidelines.

	Mammalian Cell Bank Characterization	Bacterial and Yeast Cell Bank Characterization
Identity Assays	• Karyology Services • DNA Fingerprint Assays • RAPD Assays (Random amplified polymorphic DNA)	• Viability test • API 20E • Bacteriophage Test • Gram Stain • Direct Culture • RAPD Assay • Antibiotic Resistance Test • DNA Sequence Analysis • Restriction Enzyme Mapping • Copy Number Determination • Expression Construct Retention
Purity Assays	• Electron Microscopy Services • Sterility Testing • Mycoplasma Testing • Virus Specific Assays • In vivo / in vitro Virology Assays • Retro Virology Assays • Mycobacterium Assays	
Stability Assays	• Nucleic Acid Sequencing Services • Genetic Stability Assays	
Other Assays	• Tumorgenicity • Oncogenicity	



3.3 Viral Clearance

Manufacturers of biopharmaceutical products, such as blood products, monoclonal antibodies, recombinant proteins, and medical devices are required to demonstrate their process capability to remove or inactivate viruses. Viral clearance is performed to assess the capability of the purification process to remove and/or inactivate potential viral contaminates likely to be present in or introduced during the production of biopharmaceutical products.

TFBS takes a customized approach, including advisory and regulatory support in the selection of process steps and model virus, and subsequent design of the study protocols, to ensure a successful program to be established and performed based upon clients' schedule. Customized study is also available in response to a variety of biopharmaceutical products and medical devices.

3.4 Bulk Lot Release Testing

Every lot of biopharmaceutical production requires a series of tests on both unprocessed and purified bulk material. All products entering domestic or global pharmaceutical markets require different tests to ensure the safety and quality of the product.

TFBS offers a wide range of safety and quality testing services for various stages of biopharmaceutical products. All assays performed are fully validated in compliance with global regulatory requirements such as FDA, EMA, and PMDA. Our experienced scientists can design a Lot Release Program base on the product attributes of your biopharmaceutical products, or we can adapt an existing program to meet your requirement.

3.5 Customized Assay Development and Analysis for Preclinical/Clinical Samples

TFBS provides a wide range of services to support assay development from early drug discovery, preclinical development, to clinical stage.

Our scientists support assay development to investigate drug potency related activity in vitro and in vivo at different stages, such as assay development, optimization, and validation. We have experiences in supporting different medicinal products, including biologics, vaccines, cell and gene therapy. Our dedicated and experienced scientists are very competent in developing different product-specific assays in a timely and cost-effective manner.

Services for COVID Drug / Vaccine Development

∗ CDMO service (GMP)

- MCB/WCB/EOP banking
- MVS/WVS production
- Vaccine production

∗ Biosafety test (GLP/GMP)

- Cell/virus bank characterization
- Bulk harvest test

∗ Product release testing (GLP/GMP)

- Safety and impurity test
- Potency assay
- In vivo immunogenicity testing

Preclinical study (GLP)

- Proof of concept (POC) study - immunogenicity in mice
- Pilot TOX study
- Toxicity stud

∗ In vitro study for the biometrics (GLP)

- ELISPOT assay
- Anti-antigen IgA/IgG ELISA
- Cell-based nAb assay
- Cytokine profiling by ELISA or multiplex system

Be Partnered With TFBS

∗Highly Experienced and Specialized team

Provide end-to-end customized solution for every manufacturing projects.

Regular face-to-face and virtual meetings to follow-up updated information.

∗In-house full panel QC facility

Streamline the project development from beginning to completion

Integrated quality systems incorporating US, EU, and ICH cGMP requirements

∗Time-flexible and Cost-effective

Flexible time frame to meet highest customer satisfaction.

Attractive pricing while maintaining the highest quality standard

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