National Pharmaceutical Regulatory Agency (NPRA)
Ministry of Health Malaysia
Lot 36, Jalan Universiti (Jalan Profesor Diraja Ungku Aziz),
46200 Petaling Jaya, Selangor.
Tel. No. : 03-78835400
Website : http://npra.gov.my

GUIDANCE NOTE FOR CELL AND GENE THERAPY PRODUCTS (CGTPs) MANUFACTURING FACILITY IN MALAYSIA

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Good Manufacturing Practice (GMP) Section
Centre of Compliance and Quality Control
National Pharmaceutical Regulatory Agency (NPRA)
Ministry of Health Malaysia

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1.0 INTRODUCTION

This guide is established to facilitate and provide guidance for any organization or establishment in setting up a manufacturing facility for CGTPs which are regulated by NPRA. This guidance document contains the regulatory process description and type of inspection involved for CGTPs manufacturing facility as well as the frequently asked questions (FAQs).

Note:
This guide is issued to replace the Guidance Note for Biological Products Facility Establishment in Malaysia, Second Edition, 1 October 2017.

2.0 SCOPE

2.1 The scope of this guidance note is **only applicable to Class II CGTPs: Higher risk cell therapy products.**

2.2 This guidance note excludes **Class I CGTPs: Lower risk cell therapy products** since this class of CGTPs is not regulated by NPRA.

3.0 GUIDELINES IN USE

Applicants must be fully aware and understand the legal requirements and guidelines used in initiating the set-up of a CGTPs manufacturing facility in Malaysia. For this purpose, this guidance note enlisted the related regulations and guidelines for reference.

3.1 Regulations

i. Sales of Drugs Act 1952

ii. Control of Drugs and Cosmetics Regulations 1984 (CDCR 1984)

iii. Directive and Guidelines issued under Regulations 29, CDCR 1984

- *Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 6 Tahun 2017: Direktif Kuatkuasa Perlaksanaan* Guidance Document dan Guidelines for Registration of Cell and Gene Therapy Products (CGTPs), December 2015 *dan* Good Tissue Practice Guideline, 2nd Edition, December 2015; 29 May 2017

- *Arahan Pengarah Kanan Perkhidmatan Farmasi Bilangan 19 Tahun 2020: Direktif Berkenaan Perlaksanaan Pendaftaran Produk dan Penguatkuasaan Secara Berperingkat Bagi Produk Terapi Sel dan Gen (CGTPs) Serta Tambahan Senarai Produk Di Luar Skop Kawalan*

3.2 Guidelines

i. PIC/S Guide to Good Manufacturing Practice for Medicinal Products and its related Annexes *

ii. Drug Registration Guidance Document (DRGD)

iii. Malaysia Good Distribution Practice Guideline

iv. Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia

v. Good Tissue Practice Guideline

Note:

- *PIC/S Annexes related to CGTPs including:
  - Annex 1 Manufacture of Sterile Medicinal Products
  - Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use
  - Annex 8 Sampling of Starting and Packaging Materials
  - Annex 11 Computerized Systems
  - Annex 15 Qualification and Validation
  - Annex 19 Reference and Retention Samples
  - Annex 20 Quality Risk Management
- The list is non-exhaustive. Applicants is required to refer to the latest regulations and guidelines.
- In PIC/S Guideline or some other guidelines, CGTPs also known as Advanced Therapy Medicinal Products (ATMP), so the term is interchangeable.

4.0 REGULATORY PROCESS DESCRIPTION

4.1 Facility Layout Submission

Applicant is required to submit **BPFK-503 Application for the Evaluation of Manufacturing Plant Layout** along with the required supporting documents as stated in the application form and respective processing fee (RM 1,000 for evaluation of new layout and RM 500 for evaluation of amended approved layout).

4.2 Preparation of Pharmaceutical Quality System (PQS)

Upon the facility layout and other authorities' approval, applicant may begin the set-up of the PQS for the manufacture of CGTPs according to the guidelines stated under 3.0 of this guidance note. This includes the construction of the manufacturing facility, qualifications of equipment and utilities, establishment of relevant documentation pertaining to training and qualification of personnel, process validation, media fill, etc. including Batch Manufacturing Record (BMR) and Standard Operating Procedures

(SOPs).
Once the preparation is finalized, an inspection will be conducted on the manufacturing facility. Prior to which, applicant is required:

a) to apply online through QUEST 3+ system for Good Manufacturing Practice (GMP) Inspection with upfront payment of RM 1,000. Applicant will receive an additional invoice of the total inspection fee based on the number of inspection days and inspector(s) involved. The inspection is charged at RM 1,000/day/inspector (maximum RM 10,000) based on *Surat Kajian Semula Caj Bayaran Pemeriksaan GMP Bagi Premis Pengilang Tempatan dan Luar Negara (KK/BP09/441/239 Jld 3 [50])* dated 13 March 2007*.*

b) to provide the product classification confirmation status for the product of interest, Appendix A of this guidance note together with the relevant supporting documents listed in the Appendix for the preparation of inspection.

Note:
The processing fee imposed for the application are not refundable if the application is deemed rejected which may include incomplete supporting documents upon application.

4.3 Inspections

Once payment of the inspection fee is confirmed, inspectors will proceed with the inspection. The types of inspection conducted on CGTPs manufacturing facility, which depends on the inspection objective and product category are as follows.

a)	Pre-Certification Inspection	:	An inspection conducted on CGTPs manufacturing facility during the voluntary registration period (before year 2023).
b)	Pre-Licensing Inspection	:	An inspection conducted on CGTPs manufacturing facility for the purpose of licensing and product registration.
c)	Pre-Approval Inspection	:	An inspection conducted on additional manufacturing line/new sources of cell in an existing inspected CGTPs manufacturing facility.
d)	Routine Inspection	:	A subsequent inspection conducted on existing inspected CGTPs manufacturing facility according to a planned schedule by NPRA.

e) Verification Inspection : An inspection conducted following a punitive action. Depending on the condition, verification inspection can be combined with routine inspection.

f) Investigation Inspection : Investigation Inspection is an inspection conducted on premises based on complaint received and product recall activity.

5.0 DEPARTMENT IN-CHARGE

For any queries pertaining to this guidance note, applicants may contact;

GMP Section
Centre of Compliance and Quality Control
National Pharmaceutical Regulatory Agency
Ministry of Health Malaysia
Lot 36, Jalan Universiti (Jalan Profesor Diraja Ungku Aziz),
46200 Petaling Jaya, Selangor.

6.0 OTHERS

For matters related to licensing of the private healthcare-related facility, applicants are advised to contact *Cawangan Kawalan Amalan Perubatan Swasta* (CKAPS), Ministry of Health Malaysia.

7.0 ABBREVIATIONS

ATMP : Advanced Therapy Medicinal Products
BMR : Batch Manufacturing Record
CAPA : Corrective Action and Preventive Action Report
CDCR : Control of Drugs and Cosmetics Regulations
CGTPs : Cell and Gene Therapy Products
CKAPS : *Cawangan Kawalan Amalan Perubatan Swasta*
DCA : Drug Control Authority
DRGD : Drug Registration Guidance Document
FAQ : Frequently Asked Question
GMP : Good Manufacturing Practice
MOH : Ministry of Health, Malaysia
MREC : Medical Research and Ethics Committee
NPRA : National Pharmaceutical Regulatory Agency
PQS : Pharmaceutical Quality System
SOP : Standard Operating Procedure

8.0 FREQUENTLY ASKED QUESTIONS (FAQs)

1. Does NPRA issue a manufacturing license after the inspection?

   Manufacturing license will be issued to the manufacturing facility of CGTPs upon pre-licensing inspection with Acceptable GMP compliance status and upon valid registration of CGTPs via QUEST 3+ online system. The manufacturing license is to be applied separately via the QUEST 3+ online system and to be renewed every year.

2. Does cell and tissue establishment require an annual inspection?

   Routine inspection will be scheduled for CGTPs manufacturing facility which has previously undergone pre-licensing inspection with acceptable GMP compliance status. The subsequent routine inspection will be scheduled according to the compliance status of the previous GMP inspection.

3. Is the Class I CGTPs manufacturing facility subjected to a GMP inspection by NPRA?

   No, inspection by NPRA is only mandatory for manufacturing facility of Class II CGTPs. At this moment, Class I CGTPs are not regulated by NPRA.

4. What should I do if I have an additional line/new sources of cell in my existing inspected CGTP manufacturing facility?

   Your company is required to identify the type of changes prior notification to NPRA. For the purpose of notification to NPRA, please refer further to Drug Registration Guidance Document (DRGD), Para 2 Managing Changes of Manufacturers Facility. The type of changes involved will required different further action. Your company may also contact GMP Section, Centre of Compliance and Quality Control, NPRA for further details.

5. NPRA had performed a pre-certification inspection on February 2022, what is the validity of my GMP compliance status? When should I apply for inspection?

   The GMP compliance status is valid for 3 years starting from the date of inspection, so is valid until February 2025. * Your company can apply for GMP inspection (Pre-licensing GMP Inspection) before February of 2025.

   For your information, Pre-Certification Inspection is performed by NPRA (before year of 2023) to facilitate the industry for Stage I and II product screening in order to market their products before the year of 2025. There will

be no more Pre-Certification Inspection starting 1 January 2023.

According to Directive No. 19/2020, Class II CGTP products can only be marketed after the product is registered with Drug Control Authority (DCA) (with valid product registration number, MAL) starting 1 January 2025. Furthermore, according to CDCR 1984, no person shall manufacture, sell, supply, import or possess or administer any product **unless the product is a registered product**; and the person **holds the appropriate license** required and issued under these Regulations.

Nevertheless, your company can use the valid GMP evidence based on latest Pre-Certification Inspection for the purpose of product (CGTPs) registration. However, at the same time, your company is required to apply for Pre-Licensing Inspection to avoid any delay in manufacturing license application.

* Note: During this pandemic, remote inspection is conducted towards manufacturing premises. The validity of GMP status will be 2 years from the date of inspection.

7. What should I do if I bought over an existing CGTP manufacturing facility?

Your company is required to identify the type of changes prior notification to NPRA. For the purpose of notification to NPRA, please refer further to Drug Registration Guidance Document (DRGD), Para 2 Managing Changes of Manufacturers Facility. The type of changes involved will required different further action. Your company may also contact GMP Section, Centre of Compliance and Quality Control, NPRA for further details.

8. Who should apply for the GMP Certificate?

The manufacturer of CGTPs (which regulated by NPRA) who intends to export the CGTPs to overseas should apply for the GMP Certificate. This GMP Certificate shall be applied through QUEST 3+ online system with processing fee of RM 50/certificate.

9. How should I apply for GMP Inspection?

Your company is required to apply online through QUEST 3+ system for GMP Inspection with upfront payment of RM 1,000. Prior to that, your company is required to apply for USB token and QUEST 3+ membership.

NPRA has provided the guidance on how to apply for USB token in the NPRA website (https://www.npra.gov.my/index.php/en/regulation-basic.html).

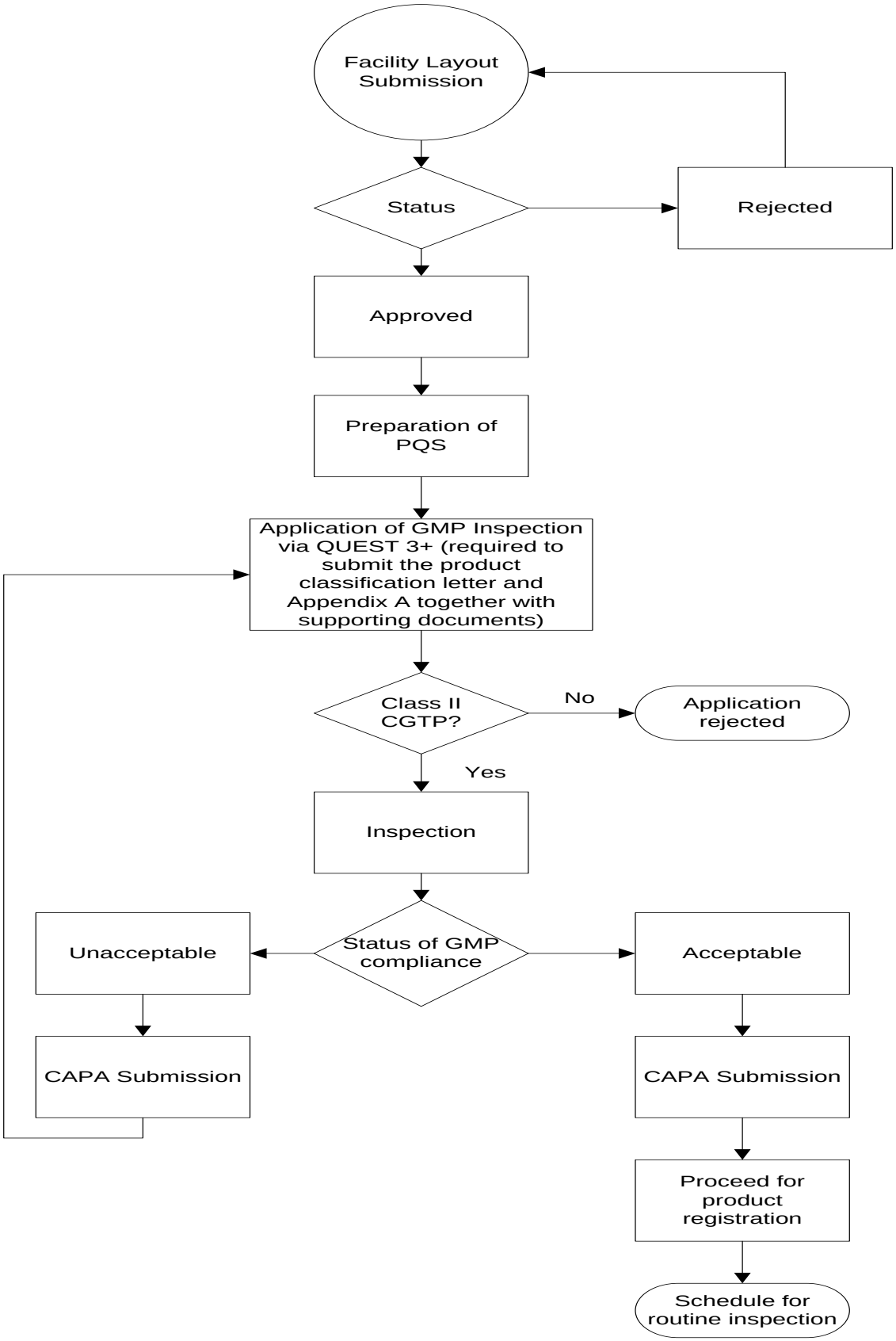
Your company may refer to the guidance provided including the USER MANUAL for QUEST Module via website (https://www.npra.gov.my/index.php/en/quest3-system-basic/user-manual-for-quest-module.html) as well as USER MANUAL QUEST 3+ System Module: Compliance and Licensing via website (https://www.npra.gov.my/images/q3plus/manual/User_Manual_Module_GMP_GDP_Inspection_Licensing.pdf) for the step wise approach on the application.

10. Who should I contact if I have further questions about CGTPs?

In relation to specific queries pertaining to CGTPs, you can contact the following Centre in NPRA;

a)	Setting up of CGTPs manufacturing facility / GMP related enquiry	:	GMP Section, Centre of Compliance and Quality Control
b)	CGTPs registration related enquiry	:	Biologics Section, Centre of Product and Cosmetic Evaluation
c)	Clinical trial related enquiry	:	Investigational Product Evaluation and Safety Section, Centre for Product and Cosmetic Evaluation
d)	Product Classification related enquiry	:	Product and Cosmetic Regulatory Coordination Section, Centre of Regulatory Coordination & Strategic Planning
e)	QUEST 3+ system related enquiry:	:	Quest Information Unit (Technical Quest), Centre of Regulatory Coordination & Strategic Planning

Figure 1: Flow Chart on Regulatory Process of New CGTPs Manufacturing Facility



APPENDIX A

PART A COMPANY AND PRODUCT DETAILS

COMPANY DETAILS			
Company Name			
Company Address			
Company Entity	☐ Government: ☐ Ministry of Health	☐ Non Ministry of Health (Please specify): _____	☐ Private
Part I (Type and Purpose of Application):			
Type of Inspection:	☐ New Source	☐ Additional source/s	☐ Others; (Please specify): _____
Type of product registration	☐ Stage I Screening	☐ Stage II Screening	☐ Full dossier
Required to be licensed by CKAPS	☐ Yes	☐ No	
Layout approved by NPRA	☐ Yes; Ref No.: _____ Date of approval: _____	☐ No	
Part II (Type of source/s):			
*please indicate different product/s name and active ingredients by semi colon (;) respectively	Product type and source	Product/s name*:	Product/s active ingredients*;
	☐ Human and/or animal source		
	☐ Animal / plant source (non-transgenic)		
	☐ Biotechnology fermentation / cell culture		
	☐ Virus or bacteria / fermentation / cell culture		
	☐ Animal sources (transgenic)		
	☐ Others; (Please specify): _____		
Part III [Activities conducted (if applicable)]:			
	☐ Collection	☐ Processing; such as manipulation, fermentation, centrifuge	☐ Others; (Please specify): _____
	☐ Fill and Finish	☐ Quality Control testing	

Part B Cell & Gene Therapy Products (CGTPs) Manufacturers

a) Facility background

i. Mandatory
☐ Site Master File
☐ NPRA's Product Classification Letter
☐ NPRA's Letter for Facility Layout Approval

ii. Optional
☐ CKAPS License
☐ Ethics Clearance e.g. MOH, MREC, University Ethics etc)
☐ NPRA's Clinical Trial Import License/ Clinical Trial Exemption
☐ Product Listing by NPRA

b) Product scope

No.	Product Name	Targeted product of interest	[a] Source	[b] Processing activities	Packaging Type	Indication	Treatment Centre - Name - Address	[c] Product Development Stages

Description & examples:

[a] Product type and source
- Human and/or animal sources
- Animal or plant source; non-transgenic
- Biotechnology fermentation / cell culture
- Virus or bacteria / fermentation / cell culture
- Animal sources; transgenic
- Others (Please specify):_____

[b] Processing activities
- Collection
- Processing
  - Process description: _____
- Fill & Finish

[c] Product Development Stages
- Pre-clinical
- Phase I / II /III / IV
- Registered