MINISTRY OF HEALTH
SINGAPORE

MH 78:04/4-2

MOH Directive No. 6/2020

13 November 2020

Licensees of Hospitals, Medical, and Dental Clinics

DIRECTIVE ON THE USE OF CELL, TISSUE AND GENE THERAPY PRODUCTS MANUFACTURED IN-HOUSE BY HEALTHCARE INSTITUTIONS

Purpose of Directive

There has been growing interest in the clinical development of cell, tissue and gene therapy products (CTGTPs),[1] which are at the forefront of scientific innovation in medicine. The Ministry of Health (MOH) has received several requests from licensed Healthcare Institutions (HCIs) to manufacture CTGTPs in-house and administer them to patients.[2] MOH is issuing this Directive pursuant to Regulation 4(1) of the Private Hospitals and Medical Clinics (PHMC) Regulations to set out the requirements that HCIs must comply with in respect of the manufacture and use of such CTGTPs. This Directive will take effect from 1 February 2021.

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1 CTGTPs refer to products containing or consisting of: (i) autologous (obtained from the same individual) or allogeneic (obtained from another individual) human cells or tissue, (ii) animal cells or tissues, or (iii) recombinant nucleic acids (modified Deoxyribonucleic Acids (DNA) or Ribonucleic Acids (RNA) as carriers of a therapeutic gene), that are, or intended to be, used for or administered to human beings for the diagnosis, treatment or prevention of human disease or conditions, or to change the appearance or anatomy of an individual.
Notwithstanding the above, CTGTPs do **not** include minimally manipulated cells or tissue that are used in:
(i) tissue and organ transplantation;
(ii) the transplantation of haematopoietic stem cells for homologous use;
(iii) blood transfusion for treating blood loss or blood disorders; and
(iv) assisted reproduction.

2 In-house manufacturing refers to non-commercial production of CTGTP by HCIs, whether for use by patients of the manufacturing HCI or to be distributed for use by patients in another HCI. It also includes the HCI "outsourcing" this manufacturing activity to a third party commercial entity to manufacture and re-supply the CTGTP back to the HCIs for use by their own patients only. In this case, the third party commercial entity should adhere to all relevant requirements stipulated by the Health Sciences Authority (HSA).

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Requirements for All HCIs Using In-house Manufactured CTGTPs

2. Licensees and registered practitioners should generally use only registered health products for patient care.

3. At present, there are only a few instances where in-house manufactured CTGTPs are generally accepted for use in the course of treatment, henceforth collectively referred to as "Generally Accepted Treatments". These are limited to the following:

(a) Autologous chondrocytes for symptomatic articular cartilage defects of the knee;
(b) *Ex vivo* expanded autologous human skin epithelial cells containing stem cells for severe burns or complex life-threatening wounds; and
(c) *Ex vivo* expanded autologous human corneal epithelial cells containing stem cells for moderate to severe limbal stem cell deficiency after eye burns.

4. In-house manufactured CTGTPs are **not** considered Generally Accepted Treatments if:

(a) the quality, safety and efficacy of such products have not been verified or ascertained;
(b) these products have not been registered with HSA; and/or
(c) they are used for therapeutic indications other than the Generally Accepted Treatments.

5. MOH would like to remind medical and dental practitioners of the requirements in the Singapore Medical Council's (SMC) 2016 Ethical Code and Ethical Guidelines (ECEG) and the Singapore Dental Council's (SDC) 2018 ECEG. In general, untested treatments that are not generally accepted by the profession can only be offered to patients in two forms: (i) in the context of formal and approved research / clinical trials; or (ii) as innovative salvage therapy. Applicable details for use of CTGTPs in research and innovative salvage therapy are found in **Annex A**.

6. In view of the potential high risk nature of CTGTPs, there are plans to introduce specific regulatory requirements for CTGTPs in treatment:

(a) licensed HCIs intending to administer CTGTPs (whether manufactured in-house or available commercially) will have to comply with licensing standards under the upcoming Healthcare Services Act, to ensure the safe administration of CTGTPs; and
(b) licensed HCIs intending to manufacture CTGTPs will also be required to comply with HSA's upcoming regulations on CTGTPs, including Guidelines on Good Manufacturing Practice for CTGTPs (HSA GMP Guidelines) where relevant,[3] under the Health Products Act.

[3] More information on HSA's CTGTP regulations can be found at: hsa.gov.sg/CTGTP

7. In the interim period, **licensed HCIs must comply with the following conditions if they are using or administering in-house manufactured CTGTPs:**

(a) **Annex B applies to <u>all</u> in-house manufactured CTGTPs**; and
(b) in addition, **Annex C applies to CTGTPs offered as innovative salvage therapy**.[4]

8. If the in-house manufactured CTGTPs are used in the research/clinical trial setting, licensed HCIs should continue to follow relevant legislative requirements. Licensed HCIs may refer to **Annex A**, to determine the applicable requirements.

Compliance with this Directive

9. To ensure that the requirements of this Directive are complied with, the Director may, at his discretion, authorise MOH officials to conduct ad-hoc compliance audits at your institutions. Please bring this Directive to the attention of your relevant staff, for their information and compliance with effect from 1 February 2021.

10. For any queries or further clarifications, please send to eLis@moh.gov.sg.

A/PROF KENNETH MAK
DIRECTOR OF MEDICAL SERVICES
MINISTRY OF HEALTH

[4] Annex C does not apply to Generally Accepted Treatments.

Use of In-House Manufactured CTGTPs in Research

1. The applicable legislation for HCIs and practitioners offering an in-house manufactured CTGTP in the research setting depends on the type of CTGTP:

(a) Human Biomedical Research Act for Class 1 CTGTPs (lower risk), which contain human cells/tissue that are:
   i. no more than minimally manipulated;[5]
   ii. intended for homologous use (i.e. used[6] for the same function as its original function and administered at the same anatomical site or histological environment in the recipient as in the donor); and
   iii. not combined or used in conjunction with a therapeutic product or medical device; or

(b) Medicines (Clinical Trials) Regulations for Class 2 CTGTPs (higher risk) i.e. CTGTPs that contain:
   i. animal cells or tissue;
   ii. recombinant nucleic acids; or
   iii. human cells or tissue that are not Class 1 CTGTP.

Use of In-house Manufactured CTGTPs as Innovative Salvage Therapy

2. Outside of the research setting, section B6 of the SMC ECEG sets out the conditions under which medical practitioners may offer an untested practice as innovative salvage therapy.

3. In the context of in-house manufactured CTGTPs that fall under this category, the following conditions would apply:

(a) Conventional therapy has proven to be unhelpful and it is a desperate or dire situation;
(b) There must be professional consensus on the use of the in-house manufactured CTGTP in the particular clinical situation; and
(c) Consent from the patients must be obtained, if they are able to give it.[7]

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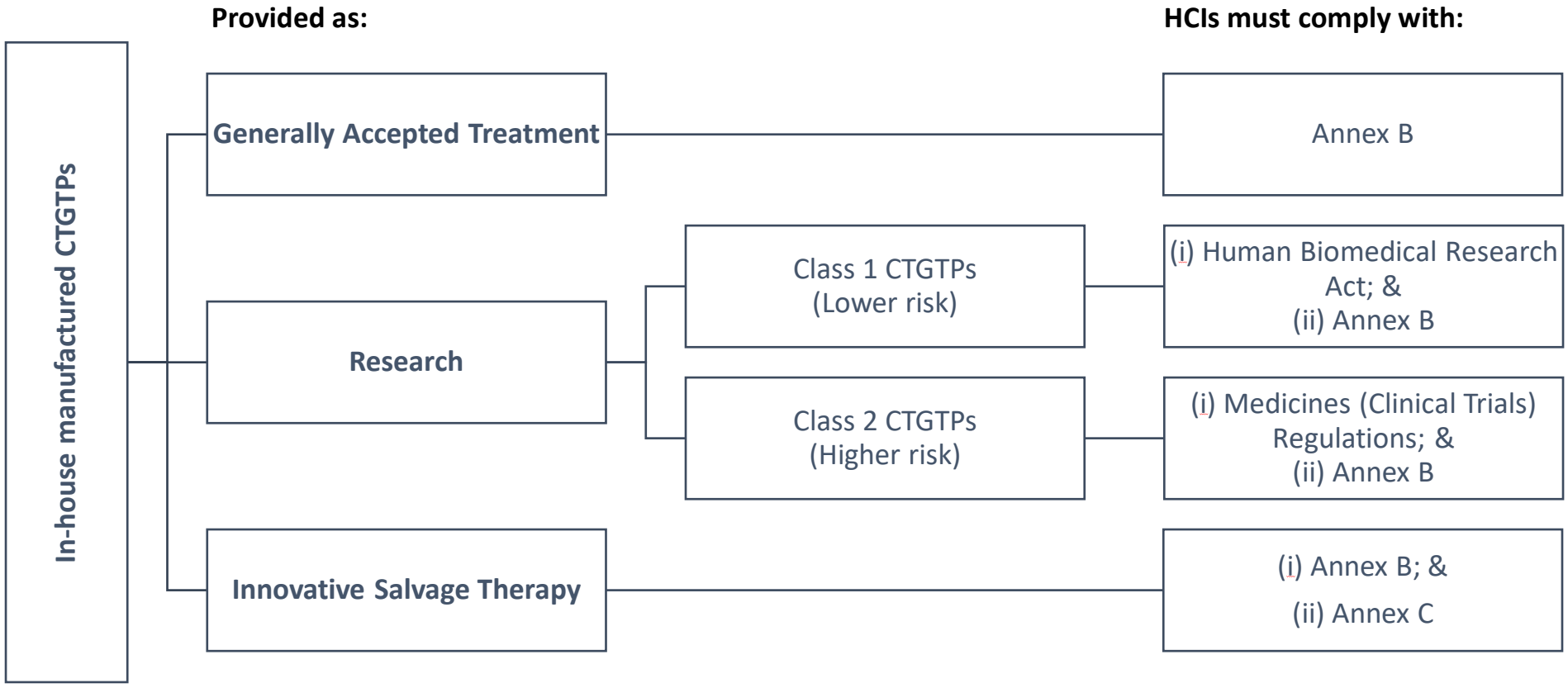
5 CTGTPs that have been processed by any of, or any combination of, the following methods, are deemed to be "minimally manipulated": cutting or sizing; grinding; shaping; centrifugation; soaking in an antibiotic or antimicrobial solution; sterilisation or irradiation; cell separation, concentration or purification; filtration; lyophilisation; freezing; cryopreservation; or vitrification – such that the biological characteristics or functions of the cell(s) or the structural properties of the tissue (as the case may be) are not altered.

6 This refers to the repair, reconstruction, replacement, or supplementation of the recipient's cells.

7 Where applicable, consent shall in addition or instead be obtained from the patient's legal guardian, as the case may be.

Summary of Relevant Requirements for HCIs Using In-House Manufactured CTGTPs



CONDITIONS FOR ALL USES OF IN-HOUSE MANUFACTURED CTGTPs

These conditions apply to all CTGTPs that had been manufactured in-house.

I. Manufacturing Standards[8]

1. To ensure sterility and quality of CTGTPs that are more than minimally manipulated, HCIs must minimally comply with the following principles of good manufacturing practices:

    a) Manufacturing of CTGTP must be carried out in the appropriate facility (e.g. clean rooms);
    b) Personnel involved in the manufacturing process must be appropriately qualified and trained, and must have a clear understanding of their tasks and responsibilities;
    c) Materials used in the manufacturing of CTGTP must be correctly identified and of the appropriate quality suitable for their intended use;
    d) Environmental monitoring must be in place to identify specific hazards causing contamination of the manufactured CTGTP and to assess the effectiveness of contamination control measures taken in mitigating the risks to patient safety;
    e) Equipment used in the manufacturing of CTGTP must be suitable for the intended use, properly cleaned and disinfected and regularly maintained; and
    f) There must be good documentation to establish, control, monitor and record all activities, and to ensure traceability.

II. Informed Consent

2. As a general guide, the patient and/or legal guardian[9] must be minimally informed of the following elements prior to consent taking:

    a) purpose of the intervention;
    b) nature of the intervention and related follow-up procedures (e.g. whether patient would require long-term special care, or other medications);
    c) that the CTGTP is manufactured 'in-house' by the HCI (not a commercial manufacturer);
    d) that the CTGTP is not registered with HSA and its safety, quality and efficacy has not been evaluated on a large scale compared to commercially available products;
    e) whether the CTGTP is approved by any other regulatory authority and the indication(s) for which is it approved for clinical use;

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8 These Manufacturing Standards will be replaced by the upcoming HSA GMP Guidelines, when it comes into force.

9 A legal guardian would ordinarily be applicable if a patient (i) lacks mental capacity, or (ii) is a minor below the age of 21 years. Where relevant, HCIs are reminded to ensure that consent taking is done in accordance to the SDC or SMC ECEG, and relevant laws such as the Mental Capacity Act and Human Biomedical Research Act.

f) possible benefits that is supportable with scientific evidence, and when the benefits would be expected to appear and measured;
g) known and potential risks that are material to the patient in his/her particular circumstances, including reported adverse events related to the CTGTP;
h) manufacturing method and potential outcomes (e.g. varying quality, efficacy or quantity may be expected);
i) details of costs to be borne by the patient, and possible sources of financial assistance (if any);[10]
j) reason(s) why alternatives such as other proven treatment are of no avail, or other research options;
k) plans for long-term monitoring / follow up (including the need for long-term submission of patient outcome data to MOH for innovative salvage therapies); and
l) how the patient's personal data will be used and stored (including for how long).

III. Standards on Personnel and Clinical Support

3. All healthcare professionals involved in the clinical management of the patient must be appropriately qualified and trained.

4. Appropriate clinical set-up must be in place to manage serious adverse events effectively (e.g. management of cytokine release syndrome, immunoglobulin replacement, availability of antidotes).

5. Appropriate systems must also be in place for long-term follow-up (i.e. for a period of at least 15 years) of patients for delayed serious adverse events that may develop (e.g. malignancies for CTGTPs that involve viral vectors).

IV. Record Keeping

6. HCIs must establish appropriate mechanisms to ensure that the CTGTP and its raw materials, including all substances that come into contact with the human cells/tissues, is traceable to the patient and/or donor (where relevant), and at all stages in the process of sourcing, manufacturing, packaging, storage, transport and delivery. HCI must keep the records for 30 years after the expiry of the CTGTP. Records must be readily available during any ad-hoc compliance audit/inspection.

7. In accordance with the 2015 National Guidelines for Retention Periods of Medical Records, HCIs must retain patients' computerised / electronic medical records for the patients' lifetime and an additional 6 years.

[10] For innovative salvage therapies, HCIs should only charge what patients would have paid for if they had undergone comparable conventional or palliative treatments. HCIs are reminded that the charging of research subjects is not allowed by MOH.

ADDITIONAL CONDITIONS FOR USE OF IN-HOUSE MANUFACTURED CTGTPs AS INNOVATIVE SALVAGE THERAPY

These conditions do not apply to the Generally Accepted Treatments, nor CTGTPs offered in the research setting.

V. Notification to MOH

8. All licensed HCIs must notify MOH of the following intent to:

    a) manufacture and/or process CTGTPs in-house; and
    b) administer in-house manufactured CTGTPs.

    HCIs must complete and submit Form A-1[11] to MOH as soon as possible. Even if a case is urgent, HCIs must make the submission at least <u>24 hours prior to the in-house manufacturing and processing of CTGTPs</u>.

9. The following documentation must be submitted to MOH together with the completed Form A-1:

    a) Relevant approvals as stipulated in paragraph 11; and
    b) Signed informed consent forms.

10. After fulfilling the requirements in Paragraphs 8 and 9 above, HCIs may proceed to administer the CTGTP to the patient. If there are any concerns, MOH will touch base with the HCI. That said, licensees and medical professionals administering in-house manufactured CTGTP are to note that they will be held accountable for ensuring the appropriate care, and safety and welfare of the patients receiving such treatments.

VI. Approvals from Relevant Committees/Authorities

11. Prior to the administration of CTGTPs that will be offered as innovative salvage therapy, agreement to offer the CTGTP to the particular patient must be obtained from the following:

    a) the HCI's tumour board, or specialty board for that particular disease condition, or at least two medical practitioners qualified to confirm the patient's dire or desperate situation under current conventional therapy and who are independent of the treatment team; and
    b) a Hospital Ethics Committee (HEC).[12]

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[11] Form A-1 is to be submitted at: https://form.gov.sg/5e295d403acc0e001141bcbe

[12] Where the HEC is unable to decide whether the proposed CTGTP is appropriate in the patient's circumstances, opinion from an expert who is familiar with the proposed CTGTP may be obtained to enable the HEC to make its decision. HCIs are reminded that they must comply with the Licensing Terms and Condition for the HEC which may be accessed at:

12. HCIs must also seek other necessary approvals from the National Environment Agency, Genetic Modification Advisory Committee, and/or MOH's Biosafety Branch, where relevant.

VII. Reporting of Serious Adverse Events

13. All serious adverse events (SAE)[13] must be reported as soon as possible, but no later than **seven calendar days** after first knowledge that a case qualifies, to HSA at https://go.gov.sg/AEreporting

VIII. Submission of Data to MOH

14. The following data must be tracked, reviewed and submitted to MOH for safety monitoring and future cost-effectiveness studies (refer to Form A-2):

    a) Patient profile;
    b) Product particulars;
    c) Mode and site of administration;
    d) Dosage and administration;
    e) Product quality attributes (e.g. identity, purity, impurity, viability, sterility, potency);
    f) Clinical outcomes (e.g. response, relapse, remission);
    g) Adverse outcomes / serious adverse events (e.g. death, cytokine release syndrome, infection, secondary tumour or other adverse events that may be of significance);
    h) Follow up period;
    i) Patient-reported outcome (e.g. health-related quality of life data); and
    j) Cost (e.g. manufacturing cost, cost for monitoring, cost of treating adverse events)

https://www.moh.gov.sg/licensing-and-regulation/regulations-guidelines-and-circulars/details/licensing-terms-and-conditions-for-hospital-ethics-committees-(issued-on-7-dec-2012)

[13] A 'Serious Adverse Event' is defined as an adverse event that:
(a) may result in a person's death;
(b) may threaten a person's life;
(c) results in a person being hospitalised or prolongs a person's existing stay in hospital;
(d) results in a person's persistent or significant disability or incapacity;
(e) results in a congenital anomaly or birth defect; or
(f) is judged to be medically important even though the effect may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the person's health or may require intervention to prevent the person's death or one of the other outcomes mentioned in (c), (d) and (e) above.

15. HCIs must complete and submit **Form A-2**[14] every 3-monthly after administration of the CTGTP for the 1st year, 6-monthly for the 2nd year, and yearly from the 3rd year onwards for a period of at least 15 years .

[14] Form A-2 may be found at: https://form.gov.sg/5e32869e0ec75e0011f2928c. Form A-2 must be submitted for each patient as specified, unless data collection is no longer feasible, e.g. in the event of patient death.