HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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CLINICAL TRIALS GUIDANCE

SUBMISSION OF INNOVATION OFFICE REQUESTS

GN-CT-17 Rev. No. 002

HSA
Health Sciences Authority

PREFACE

This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy or completeness. The Health Sciences Authority (HSA) accepts no liability for any errors or omissions in this document, or for any action / decision taken or not taken as a result of using this document. If you need specific legal or professional advice, you should consult your own legal or other relevant professional advisers.

In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.

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- Administrative changes due to HSA re-organisation

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1. INTRODUCTION

1.1. Purpose

The purpose of this document is to provide guidance to researchers, academics, biotech and pharmaceutical companies (collectively referred to in this guidance as 'sponsors') on the procedures for seeking scientific and regulatory advice from the Innovation Office. The principles outlined in this guidance ensure that all requests are managed in an effective, efficient and consistent manner, to the benefit of all parties involved in the process.

1.2. Background

The HSA Innovation Office was established to support innovation and facilitate the efficient development and timely access to innovative therapeutic products and cell, tissue and gene therapy products in Singapore. Sponsors may seek scientific and regulatory advice on their innovative product, particularly during the early phases of product development, to facilitate the planning and optimisation of product development strategies. This ensures the timely translation of scientific breakthroughs into impactful clinical treatments, ultimately delivering significant benefits to patients in Singapore and worldwide.

For more information on the Innovation Office, please visit the HSA website.

1.3. Scope

This guidance applies to requests for advice on the development of novel investigational products that are either:

(i) Therapeutic Products[1] (TPs); or

(ii) Class 2 Cell, Tissue and Gene Therapy Products (CTGTPs)[1,2].

To promote efficient use of resources, we will prioritise requests from sponsors who plan to conduct clinical trials or pursue product registration in Singapore.

For requests where product development will be pursued solely outside of Singapore, we recommend that you approach the relevant regulatory agency(ies) in the country(ies) where the clinical trial(s) will be conducted, to obtain regulatory advice.

1.4. Fees

There are no fees for engagements with the Innovation Office.

1.5. Confidentiality of submitted documents

All confidential documents submitted by the sponsors will be kept strictly confidential, in accordance with Section 66 of the Health Products Act. The Innovation Office does not enter into any non-disclosure agreements with individual sponsors.

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[1] Therapeutic Product and CTGTP are defined in the First Schedule of the Health Products Act.

[2] Class 1 and Class 2 CTGTP are defined in the Health Products (Cell, Tissue and Gene Therapy Products) Regulations.

- Class 1 CTGTP means a CTGTP that —
  - (a) is the result of only minimal manipulation of human cell or tissue;
  - (b) is intended for homologous use;
  - (c) is not combined or used with a therapeutic product or a medical device; and
  - (d) is assigned by HSA as a Class 1 CTGTP due to a lower health risk to a user of the product.
- Class 2 CTGTP means a CTGTP other than a Class 1 CTGTP.

2. GUIDANCE

2.1. Useful resources for sponsors

Before requesting a meeting with the Innovation Office, you are strongly advised to review the following publicly available guidelines provided by HSA, the International Council for Harmonisation (ICH), and other regulatory agencies, such as the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA), where applicable. The list provided below is non-exhaustive, and you are encouraged to refer to other relevant guidelines that may address your specific product development needs.

Should you have further questions after consulting these resources, you may submit a request for advice to the Innovation Office, following the procedures outlined in Section 2.2.

2.1.1. General HSA Guidance Documents

- HSA guidances on the conduct of clinical trials in Singapore

2.1.2. Guidelines relevant for Therapeutic Products

Nonclinical Guidelines

- ICH M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals
- ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

Clinical Guidelines (For First-In-Human Clinical Trials)

- EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products
- FDA Guidance: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

Chemistry, Manufacturing and Controls (CMC) Guidelines:

- EMA Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials
- EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

2.1.3. Guidelines relevant for Cell, Tissue and Gene Therapy Products

HSA Guidance Documents

- HSA Guidance on the chemistry, manufacturing and controls requirements for cell, tissue or gene therapy product for clinical trials and product registration (Appendix 8 of CTGTP registration guide)

Other Regulatory Guidelines

- EMA Guideline on quality, nonclinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials
- FDA Guidance: Preclinical Assessment of Investigational Cellular and Gene Therapy Products
- FDA Guidance: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- FDA Guidance: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products
- FDA Guidance: Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products
- FDA Guidance: Human Gene Therapy Products Incorporating Human Genome Editing

2.2. Procedures

2.2.1. Submitting a request for advice

You may seek advice from the Innovation Office on one or more of the following, in relation to the development of an innovative product:

(i) Nonclinical studies required to support clinical development;
(ii) Clinical trial design and clinical development plans;
(iii) Chemistry, manufacturing and controls (CMC);
(iv) Manufacturing requirements.

You are requested to write in to HSA_InnovationOffice@hsa.gov.sg.

Your request should be accompanied by the submission of the following:

(i) IO Request Form (see Appendix A);
(ii) Briefing Document, which should include:
    a) Adequate background information and product description;
    b) List of questions for HSA, and a succinct explanation of the sponsor's position or proposal for each question, with appropriate justifications (see Section 3 below);
    c) Supporting information relevant to addressing the questions (see Section 4 below).
(iii) Scientific advice from other regulatory authority(ies), if any.

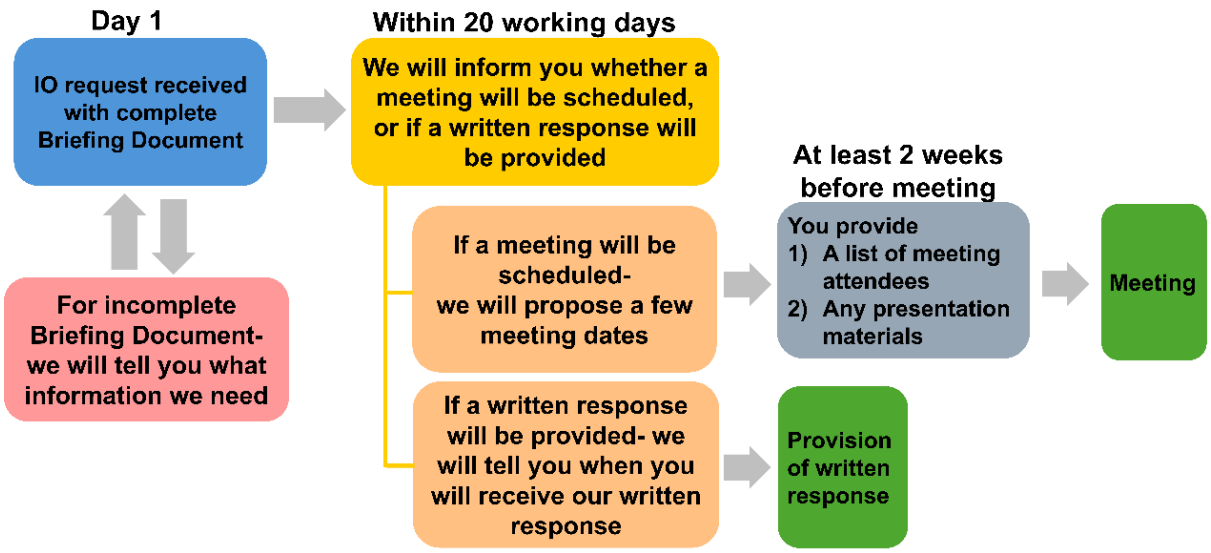
2.2.2. Assessing the need for a meeting and format of meetings

Interactions with Innovation Office can take one or more of the following formats:

(i) Face to face – these are in-person meetings that are held at HSA's premises;
(ii) Online meetings – these meetings are conducted remotely and can accommodate both local and overseas attendees;
(iii) Written response – where a meeting is not required, the Innovation Office will provide HSA's consolidated responses to the sponsor's questions in writing, via email.

While you can request for a meeting with HSA, we will assess each request and review the supporting documents, before deciding on the need for a meeting. In general, a meeting may be granted if there are questions or issues that may benefit from further discussion with you. For questions that are relatively straightforward to address, we may provide a written response to your questions.

2.2.3. HSA's response timelines to meeting requests



Once you have submitted your request, we will inform you within 20 working days of receiving a complete Briefing Document whether a meeting will be scheduled, or if a written response will be provided. This decision will be based on the complexity of your questions. If your request may benefit from further discussion, we may propose a meeting to discuss the details of your request in depth. The 20-day timeframe is for us to inform you whether a meeting will be arranged, or if not needed, the estimated timeline for receiving HSA's written response. A meeting will not be scheduled during this period.

If a meeting is proposed, we will contact you to schedule a meeting date. You will be requested to provide the following information at least 2 weeks before the confirmed meeting date:

(i) List of meeting attendees, including their names and designations.

(ii) Any presentation materials summarising the questions for HSA, and key information from the Briefing Document that are relevant to the questions asked.

If a meeting is not required, we will provide you with an estimated timeline for providing HSA's written response. This estimated timeline will be communicated to you within 20 working days of receiving a complete Briefing Document.

While we aim to provide a response to sponsors within the timeline stipulated above, you should note that the response timeline may be delayed should the information provided be insufficient or lack proper context, or where new questions and/or information are added after we have commenced review.

2.2.4. Subsequent request(s) for advice

Following conclusion of the initial request for advice, you may engage the Innovation Office again for further regulatory advice on the same investigational product at a later stage of development. This will be treated as a new request from you and should follow the procedures outlined above in this guidance document.

3. LIST OF SPECIFIC QUESTIONS FOR HSA

The Innovation Office request should include a list of questions grouped by disciplines (e.g., nonclinical, clinical, CMC, manufacturing requirements). For each question, you should provide a succinct explanation of your position or proposal and why you consider it acceptable. This explanation may refer to supporting information in the Briefing Document, as relevant.

3.1. Examples of questions that are clear and focused

Your questions should be clear and specific so that we can provide advice targeted to your questions. If your questions are too broad or general, our response may also be general. Questions should ideally be posed in a such a way that we can either agree or disagree with a proposed plan. The following are examples of clear and focused questions.

3.1.1. Nonclinical

(i) Does HSA agree that the proposed in vitro and in vivo proof-of-concept (POC) studies are adequate to support the conduct of the proposed clinical trial?

(ii) Does HSA agree that the proposed biodistribution and toxicology studies are acceptable?

(iii) Does HSA agree that the study design for the definitive toxicology study is adequate?

(iv) Does HSA agree that the overall preclinical programme is adequate to support the proposed Phase 1 clinical trial?

3.1.2. Clinical

(i) Does HSA agree with the key elements of the proposed clinical trial design?

(ii) Is the study population, as described in the eligibility criteria, appropriate for the proposed first-in-human (FIH) study?

(iii) Does HSA agree with the approach used to determine the proposed starting dose and dose-escalation plan in the proposed Phase 1 trial?

(iv) Does HSA agree that the study objectives, design and endpoints are acceptable for the FIH study?

3.1.3. Chemistry, Manufacturing and Controls (CMC)

(i) Does HSA agree with the manufacturing process and control strategy?

(ii) Does HSA agree that the testing and characterization of the cell banks are adequate?

(iii) Does HSA agree with the proposed release specifications and testing strategy?

(iv) Does HSA agree with the stability testing of the drug substance and drug product?

3.2. Examples of questions that are considered too general

Questions such as those listed below are considered too broad and are therefore discouraged. By framing questions with more context and specificity, you can facilitate more effective and focused discussions.

(i) What nonclinical studies are needed to support a First-in-Human study?

(ii) Is GMP required for this study?

(iii) How do I choose a GMP manufacturer for my product?

4. BRIEFING DOCUMENT

4.1. Purpose of the Briefing Document

Your Briefing Document should include adequate background information and product description. In addition, supporting information relevant for addressing your questions should be included. Your Briefing Document should be structured, well-organised, and paginated with relevant information presented in a manner for easy reference, and ideally accompanied by a table of contents (see Appendix B for a suggested format for the Briefing Document). Please refrain from submitting separate publications as the Briefing Document; instead, summarise in the Briefing Document the pertinent and specific aspects from the publications that are relevant to the context of the questions asked. Wherever possible, summarise and interpret

raw data rather than including it in its entirety. This approach will facilitate a more efficient and thorough review by HSA.

4.2. Example of product description and background information that may be included in the Briefing Document

(i) A description of your product and active ingredient
(ii) Mechanism of action
(iii) Proposed therapeutic indication
(iv) Dosage form, route of administration and dosing regimen
(v) Background information on your product development and the request for scientific advice

4.3. Example of supporting information that may be included in the Briefing Document

The following are examples of information that may be included in your Briefing Document, depending on your specific questions to HSA.

4.3.1. Nonclinical

(i) Summary of all planned and completed preclinical studies (in vitro and in vivo studies) including the rationale and purpose of each study in the context of the overall nonclinical programme. These studies should collectively demonstrate the mechanism of action, safety, and potential efficacy to support the proposed clinical trial
(ii) Similarities and differences between the nonclinical product lot(s) used and the intended clinical lot. For any differences, please discuss how this impacts interpretation of the nonclinical data.
(iii) The rationale for the design of individual definitive preclinical safety/toxicology studies, and sufficient information on study methodology (e.g., choice of animal species/models, choice of control groups, dose levels, dosing schedule and procedure, timing and choice of study endpoints, duration of follow-up)
(iv) A statement of compliance to GLP for key safety studies. For each safety/toxicology study that was not conducted in compliance with GLP,

the reason for the noncompliance, including the areas of deviation and any impact to the reliability of the study results should be provided to HSA.

4.3.2. Clinical

(i) Prior clinical experience, if any

(ii) Clinical trial protocol synopsis or draft protocol that includes, but is not limited to:

a) trial design
b) objectives
c) intended patient population (e.g., age, severity of disease, phenotype)
d) eligibility criteria
e) justification for proposed dose(s)
f) dosing regimen
g) delivery procedure, including device (as applicable)
h) study assessments and monitoring plan
i) safety and preliminary efficacy endpoints (e.g., outcome measures)

4.3.3. CMC

(i) Description of the product, manufacturing process and testing conducted (in-process / final product) to demonstrate product identity, quality, and safety

(ii) Description of product formulation and storage conditions

(iii) Discussion of product stability

(iv) Detailed descriptions of any CMC issues on which feedback is being requested (e.g., sourcing of starting materials, potency assessment)

(v) Brief discussion of the manufacturing facility, and steps taken to ensure product segregation and tracking

(vi) Discussion of the starting materials and control of the starting materials

(vii) Description of devices that will be used for product administration or cell selection

5. APPENDICES

(i) Appendix A – Innovation Office Request Form [GN-CT-17A]

(ii) Appendix B – Suggested format for the Briefing Document [GN-CT-17B]

HEALTH SCIENCES AUTHORITY

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Blood Services Group
Enforcement Group
Integrated Health Regulation Group

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