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HEALTH PRODUCTS ACT
(CHAPTER 122D)

HEALTH PRODUCTS (THERAPEUTIC PRODUCTS AS CLINICAL RESEARCH MATERIALS) (AMENDMENT) REGULATIONS 2021

In exercise of the powers conferred by sections 71(1) and 72(1) of the Health Products Act, the Health Sciences Authority, with the approval of the Minister for Health, makes the following Regulations:

Citation and commencement

1. These Regulations are the Health Products (Therapeutic Products as Clinical Research Materials) (Amendment) Regulations 2021 and come into operation on 1 March 2021.

Amendment of regulation 1

2. Regulation 1 of the Health Products (Therapeutic Products as Clinical Research Materials) Regulations 2016 (G.N. No. S 332/2016) (called in these Regulations the principal Regulations) is amended by deleting the words "Therapeutic Products as".

Amendment of regulation 2

3. Regulation 2(1) of the principal Regulations is amended —

(*a*) by inserting, immediately before the definition of "administer", the following definition:

" "active substance", in relation to a CTGT product, means a substance that —

(*a*) is usable in the manufacture of a CTGT product as an active constituent; and

(*b*) achieves its intended action by pharmacological, immunological, physiological, metabolic or physical means;";

(*b*) by deleting the definition of "appropriate non-proprietary name" and substituting the following definition:

" "appropriate non-proprietary name", in relation to an active ingredient of a therapeutic product or an active substance in a CTGT product, means —

(*a*) the name or a synonym of the active ingredient or the active substance (as the case may be) described in the relevant monograph appearing in the latest edition of any specified publication; or

(*b*) in any other case, its international non-proprietary name or the accepted scientific name or other name descriptive of the true nature of the active ingredient or the active substance, as the case may be;";

(*c*) by deleting the definition of "clinical research material" and substituting the following definition:

" "clinical research material" means any of the following that is manufactured, imported or supplied for the purpose of being used in any clinical research by way of administration to a subject in accordance with the protocol for the research:

(*a*) a therapeutic product;

(*b*) a CTGT product that is treated as a Class 1 CTGT product under the CTGTP Regulations and for which no notice has been submitted under

regulation 4, 7 or 10 (as the case may be) of the CTGTP Regulations;

(*c*) a CTGT product that is treated as a Class 2 CTGT product under the CTGTP Regulations;

(*d*) a placebo;";

(*d*) by inserting, immediately after the definition of "codeine cough preparation", the following definitions:

" "CTGT product" means a health product categorised as a cell, tissue or gene therapy product in the First Schedule to the Act;

"CTGTP Regulations" means the Health Products (Cell, Tissue and Gene Therapy Products) Regulations 2021 (G.N. No. S 104/2021);";

(*e*) by inserting, immediately after the definition of "institutional review board", the following definition:

" "international non-proprietary name", for an active ingredient of a therapeutic product or an active substance in a CTGT product, means a name which has been selected by the World Health Organization as a recommended international non-proprietary name for the active ingredient or the active substance, as the case may be;"

(*f*) by inserting, immediately after the definition of "in-store pharmaceutical officer", the following definition:

" "licensed healthcare institution" means a healthcare institution that is licensed under the Private Hospitals and Medical Clinics Act (Cap. 248);";

(*g*) by inserting, immediately after the words "therapeutic product" in the definition of "prescription-only medicine", the words "or a CTGT product";

(*h*) by deleting the definition of "proprietary name" and substituting the following definition:

" "proprietary name" means a word or words used in connection with the supply of a therapeutic product or CTGT product for the purpose of indicating that it is the product of a particular person who manufactures, selects the name of, certifies or deals with that product, or offers it for supply;";

(*i*) by inserting, immediately after the definition of "regulated clinical trial", the following definition:

" "specified publication" means any of the following:

(*a*) the British Pharmacopoeia;

(*b*) the European Pharmacopoeia;

(*c*) the United States Pharmacopoeia and the National Formulary;

(*d*) any other publication that is specified on the Authority's website;"; and

(*j*) by deleting the full-stop at the end of the definition of "therapeutic product" and substituting a semi-colon, and by inserting immediately thereafter the following definition:

" "traceability", in relation to a CTGT product, means —

(*a*) the ability to locate and identify the CTGT product and its starting and raw materials at any point in time during its manufacture, import, supply or administration, including the sourcing, procurement, processing, testing, packaging, storage, transport, delivery and disposal of the CTGT product;

(*b*) the ability to identify the donor and tissue bank, blood bank or manufacturing facility that receives, processes or stores any cells or tissue that the CTGT product contains;

(*c*) the ability to locate and identify all data relating to any raw material or other substance that comes into contact with any cells or tissue that the CTGT product contains; and

(*d*) the ability to identify the person who receives the CTGT product at a licensed healthcare institution or a licensed retail pharmacy at which the CTGT product is administered, dispensed or supplied to a subject.".

Amendment of regulation 5

4. Regulation 5(1) of the principal Regulations is amended by inserting, immediately after the words "clinical research material that", the words "is a therapeutic product and that".

Amendment of regulation 6

5. Regulation 6(1) of the principal Regulations is amended by deleting the words "clinical research material which" and substituting the words "clinical research material that is a therapeutic product and that".

Amendment of regulation 10

6. Regulation 10(1) of the principal Regulations is amended by inserting, immediately after the words "clinical research material that is a", the words "therapeutic product and".

New regulation 14A

7. The principal Regulations are amended by inserting, immediately after regulation 14, the following regulation:

"**Duty to maintain system of traceability for CTGT product**

14A.—(1) Every manufacturer, importer, supplier or registrant of clinical research material that is a CTGT product must establish and maintain a system of traceability that complies with paragraph (2).

(2) The system mentioned in paragraph (1) must at the minimum enable the traceability of the CTGT product and its starting and raw materials, including all substances that may come into contact with the cells or tissue it contains, during any of the following processes:

(*a*) sourcing;

(*b*) procurement;

(*c*) processing;

(*d*) testing;

(*e*) packaging;

(*f*) storage;

(*g*) transport;

(*h*) delivery to the clinical research site where the CTGT product is used, administered, supplied or dispensed, as the case may be;

(*i*) any other final reconciliation, disposal or destruction of the CTGT product.

(3) Every supplier must ensure that a system of traceability is in place and maintained at the clinical research site in order that the CTGT product administered or supplied may be linked to the patient who received it, and vice versa.

(4) Every manufacturer, importer or supplier mentioned in paragraphs (1) and (3) must keep all data obtained from the system of traceability for at least 30 years after the expiry date of the CTGT product or any other shorter period that the Authority allows in a particular case.".

Deletion and substitution of regulation 15

8. Regulation 15 of the principal Regulations is deleted and the following regulation substituted therefor:

"**Records of manufacture**

15. A manufacturer must keep the following records:

(*a*) in the case of a manufacturer of clinical research material — records of the manufacture, assembly and testing of the material;

(*b*) in the case of a manufacturer of clinical research material that is a CTGT product — records of traceability.".

Amendment of regulation 16

9. Regulation 16(1) of the principal Regulations is amended by deleting the words "and traceability".

Amendment of regulation 17

10. Regulation 17(1) of the principal Regulations is amended by deleting the words "and traceability".

Amendment of regulation 18

11. Regulation 18 of the principal Regulations is amended —

(*a*) by deleting paragraph (2) and substituting the following paragraph:

"(2) For records relating to any manufacture, assembly and testing of clinical research material, the applicable period is as follows:

(*a*) in the case of registered and unregistered investigational clinical research material and unregistered auxiliary clinical research material — 5 years after the completion or discontinuation of the last clinical trial in which the batch of that material was used;

(*b*) in the case of registered auxiliary clinical research material, the longer of the following periods:

(i) one year after the expiry date of the material;

(ii) 5 years after the date of such manufacture, assembly and testing;

(*c*) in the case of traceability records relating to clinical research material that is a CTGT product — 30 years after the expiry date of the product or any other shorter period that the Authority allows in a particular case.”; and

(*b*) by deleting sub-paragraph (*a*) of paragraph (3) and substituting the following sub-paragraph:

“(*a*) where the clinical research is not a regulated trial and —

(i) the clinical research material is not a CTGT product — 2 years after the supply, putting to some other use, disposal or export, as the case may be; or

(ii) the clinical research material is a CTGT product and —

(A) the records do not relate to traceability — 2 years after the supply, putting to some other use, disposal or export, as the case may be; or

(B) the records relate to traceability — 30 years after the expiry of the CTGT product, or any other shorter

period that the Authority allows in a particular case;".

Amendment of regulation 19

12. Regulation 19(3) of the principal Regulations is amended by deleting the words "of an investigator of any clinical research that is not a regulated clinical trial," in the definition of "investigator's brochure".

New regulation 19A

13. The principal Regulations are amended by inserting, immediately after regulation 19, the following regulation:

"**Duty to report defects**

19A. For the purposes of section 42(1)(*a*) of the Act, every manufacturer, importer or supplier of any clinical research material must report any defect in the clinical research material to the Authority within the following period after the manufacturer, importer or supplier (as the case may be) first becomes aware of the defect:

(*a*) if the defect represents a serious threat to persons or public health, within 48 hours;

(*b*) in all other cases, within 15 days.".

Amendment of regulation 20

14. Regulation 20(1) of the principal Regulations is amended by deleting the words "which the person manufactured, imported or supplied pursuant to regulation 3".

Amendment of regulation 21

15. Regulation 21 of the principal Regulations is amended —

(*a*) by deleting paragraph (1) and substituting the following paragraph:

"(1) The Authority may, on the application of —

(*a*) a manufacturer of any clinical research material; or

(*b*) a manufacturer of an active substance or a starting material used in the manufacture of clinical research material that is a CTGT product,

and on being satisfied, after completing an assessment of conformity, that the manufacturer conforms to an applicable Good Manufacturing Practice Standard, issue a GMP Certificate to the manufacturer subject to any terms and conditions as the Authority thinks fit."; and

(*b*) by deleting the definition of "Good Manufacturing Practice Standard" in paragraph (4) and substituting the following definition:

" "Good Manufacturing Practice Standard" means any of the following as shown on the Authority's website:

(*a*) for therapeutic products —

(i) the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme Guide to Good Manufacturing Practice for Medicinal Products; or

(ii) any other good manufacturing practice standard approved by the Authority;

(*b*) for CTGT products —

(i) the Good Manufacturing Practice Standard for CTGT products issued by the Authority; or

(ii) any other good manufacturing practice standard that is approved by the Authority.".

Amendment of regulation 22

16. Regulation 22(1) of the principal Regulations is amended by inserting, immediately after the words "therapeutic product", the words "or CTGT product".

Amendment of regulation 24

17. Regulation 24 of the principal Regulations is amended —

(*a*) by deleting the words "15, 16(1), (3), (4) or (5), 17(1), 18(1), 19(1) or (2)," in paragraph (1)(*a*) and substituting the words "14A(1), (3) or (4), 15, 16(1), (3), (4) or (5), 17(1), 18(1), 19(1) or (2), 19A,"; and

(*b*) by inserting, immediately after the word "regulation" in paragraph (2), the words "14A(1), (3) or (4),".

Amendment of First Schedule

18. The First Schedule to the principal Regulations is amended —

(*a*) by inserting, immediately after the word "documents" in item 2, the words "for a therapeutic product"; and

(*b*) by inserting, immediately after item 2, the following item:

"3. Application fee for each of the following certificates or documents for a CTGT product, or an active substance or starting material used in the manufacture of a CTGT product:

(*a*) a GMP Certificate (with technical assessment)	$22,000
(*b*) a GMP Certificate (without technical assessment)	$210
(*c*) a GDP Certificate (with technical assessment)	$3,700
(*d*) a GDP Certificate (without technical assessment)	$210

".

Amendment of Second Schedule

19. Part 1 of the Second Schedule to the principal Regulations is amended by inserting, immediately before the words "the supply" in sub-paragraph (ii) in the second column of item 1(*b*), the words "for therapeutic products only".

Amendment of Third Schedule

20. The Third Schedule to the principal Regulations is amended —

(*a*) by deleting the word "traceability" in paragraph 1(1)(*a*) and substituting the words "product tracking";

(*b*) by deleting the words "the name of the substance used in the clinical research material" in paragraph 1(2)(*e*) and substituting the words "in the case of clinical research material that is a therapeutic product, the name of the substance used in the therapeutic product";

(*c*) by inserting, immediately after sub-paragraph (*e*) of paragraph 1(2), the following sub-paragraph:

"(*ea*) in the case of clinical research material that is a CTGT product, the name of the CTGT product and a description, expressed qualitatively and quantitatively, of any active substance in the CTGT product, as well as, in the case of blinded trials, the name of the comparator or placebo;";

(*d*) by deleting the full-stop at the end of sub-paragraph (*j*) of paragraph 1(2) and substituting a semi-colon, and by inserting immediately thereafter the following sub-paragraphs:

"(*k*) in the case of clinical research material that is an autologous CTGT product, the unique patient identifier and the words "for autologous use only" or similar wordings;

(*l*) in the case of clinical research material that is a CTGT product, the list of excipients, including preservative systems (if applicable), for the CTGT product;

(*m*) in the case of clinical research material that is a CTGT product, any warning that is necessary for the CTGT product;

(*n*) in the case of clinical research material that is a CTGT product, any precaution relating to the disposal of any unused CTGT product or any waste derived from the CTGT product (where appropriate) and any available collection system for the unused CTGT product or waste.";

(*e*) by deleting the word "and" in paragraph 1(3)(*e*) and substituting the word "or";

(*f*) by deleting sub-paragraph (*f*) of paragraph 1(3) and substituting the following sub-paragraphs:

"(*f*) in the case of clinical research material that is a therapeutic product, where the appropriate non-proprietary name is included on the name of the label of the product, the appropriate quantitative particulars of any active ingredient of the product;

(*fa*) in the case of clinical research material that is a CTGT product, the name of the CTGT product and a description, expressed qualitatively and quantitatively, of any active substance in the CTGT product;";

(*g*) by deleting the full-stop at the end of sub-paragraph (*k*) of paragraph 1(3) and substituting a semi-colon, and by inserting immediately thereafter the following sub-paragraphs:

"(*l*) the conditions under which the clinical research material must be stored;

(*m*) in the case of clinical research material that is an autologous CTGT product, the unique patient identifier and the words "for autologous use only" or similar wordings;

(*n*) in the case of clinical research material that is a CTGT product, the list of excipients, including preservative systems (if applicable), for the CTGT product;

(*o*) in the case of clinical research material that is a CTGT product, any warning that is necessary for the CTGT product;

(*p*) in the case of clinical research material that is a CTGT product, any precaution relating to the disposal of any unused CTGT product or any waste derived from the CTGT product (where appropriate) and any available collection system for the unused CTGT product or waste.";

(*h*) by deleting the word "and" in paragraph 1(4)(*c*) and substituting the word "or";

(*i*) by deleting sub-paragraph (*d*) of paragraph 1(4) and substituting the following sub-paragraphs:

"(*d*) in the case of clinical research material that is a therapeutic product, where the appropriate non-proprietary name is included on the name of the label of the product, the appropriate quantitative particulars of any active ingredient of the product;

(*da*) in the case of clinical research material that is a CTGT product, the name of the CTGT product and a description, expressed qualitatively and quantitatively, of any active substance in the CTGT product;";

(*j*) by deleting the full-stop at the end of sub-paragraph (*i*) of paragraph 1(4) and substituting a semi-colon, and by inserting immediately thereafter the following sub-paragraphs:

"(*j*) the conditions under which the clinical research material must be stored;

(*k*) in the case of clinical research material that is an autologous CTGT product, the unique patient identifier and the words "for autologous use only" or similar wordings;

(*l*) in the case of clinical research material that is a CTGT product, the list of excipients, including preservative systems (if applicable), for the CTGT product;

(*m*) in the case of clinical research material that is a CTGT product, any warning that is necessary for the CTGT product;

(*n*) in the case of clinical research material that is a CTGT product, any precaution relating to the disposal of any unused CTGT product or any waste derived from the CTGT product (where appropriate) and any available collection system for the unused CTGT product or waste.";

(*k*) by inserting, immediately after the words "(if registered)" in paragraph 1(5)(*c*), the words "or in accordance with the notice submitted to the Authority under regulation 16 of the CTGTP Regulations";

(*l*) by deleting the words "sub-paragraph (2)(*b*), (*c*), (*d*) and (*f*) to (*i*)" in paragraph 1(8) and substituting the words "sub-paragraphs (2)(*b*), (*c*), (*d*) and (*f*) to (*i*), (3)(*a*), (*b*), (*d*), (*g*), (*j*) and (*k*) and (4)(*b*), (*e*), (*h*) and (*i*)";

(*m*) by inserting immediately after sub-paragraph (9) of paragraph 1, the following sub-paragraph:

"(10) In this paragraph —

"autologous", in relation to a CTGT product, means a CTGT product that contains cells or tissue that are obtained only from the individual to whom the CTGT product is to be administered;

"registered auxiliary CRM" and "registered investigational CRM" include auxiliary clinical research material or investigational clinical research material (as the case may be) that is treated as a Class 1 CTGT product under the CTGTP Regulations and for which a notice under regulation 16 of the CTGTP Regulations has been submitted to the Authority;

"unregistered auxiliary CRM" and "unregistered investigational CRM" include auxiliary clinical research material or investigational clinical research material (as the case may be) that is treated as a Class 1 CTGT product under the CTGTP Regulations and for which a notice under regulation 16 of the CTGTP Regulations has not been submitted to the Authority."; and

(*n*) by deleting paragraph 2.

Miscellaneous amendments

21. The principal Regulations are amended —

(*a*) by deleting the words "therapeutic products" in the following provisions and substituting in each case the words "therapeutic products or CTGT products":

Regulation 9(3)(*b*)

Regulation 14(4)(*b*); and

(*b*) by deleting the words "THERAPEUTIC PRODUCTS" in the heading of Part 1 of the Second Schedule and substituting the words "THERAPEUTIC PRODUCTS OR CTGT PRODUCTS".

[G.N. No. S 94/2019]

Made on 15 February 2021.

KANDIAH SATKUNANANTHAM
Chairman,
Health Sciences Authority,
Singapore.

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(To be presented to Parliament under section 72(5) of the Health Products Act).