INVITED SUBMISSION

Clinical Translation of Cell Therapy, Tissue Engineering, and Regenerative Medicine Product in Malaysia and Its Regulatory Policy

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With the worldwide growth of cell and tissue therapy (CTT) in treating diseases, the need of a standardized regulatory policy is of paramount concern. Research in CTT in Malaysia has reached stages of clinical trials and commercialization. In Malaysia, the regulation of CTT is under the purview of the National Pharmaceutical Control Bureau (NPCB), Ministry of Health (MOH). NPCB is given the task of regulating CTT, under a new Cell and Gene Therapy Products framework, and the guidelines are currently being formulated. Apart from the laboratory accreditation, researchers are advised to follow Guidelines for Stem Cell Research and Therapy from the Medical Development Division, MOH, published in 2009.

Introduction

SINCE THE INTRODUCTION of cell therapy and tissue engineering, the regulatory issue of translating products from the laboratory to the bedside involves a serious discussion between the researcher, clinician, and regulatory body. Despite the uncertain economic future of cell and tissue therapy (CTT), cell therapy companies continue to rise.¹ The regulatory framework for the CTT product is becoming more stringent as indicated by an increase in number of Good Manufacturing Practice (GMP) facilities in Europe, as shown by a survey done in 2010.² In the United States, the Food and Drug Administration (USFDA),³ and in Europe, CTT, regulate CTT through a centralized procedure by the European Medicines Agency (EMA) under Advanced Therapy Medicinal Products (ATMPs) since 2008.^{3–6} In Asia, CTT is regulated by various regulatory agencies, such as Japan Pharmaceuticals and Medical Devices Agency (PMDA), Ministry of Food and Drug Safety (MFDS) in South Korea, and the Health Sciences Authority (HSA) in Singapore.⁶

In Malaysia, where the economy is mainly driven by its natural products and labor-intensive industries, biotechnology is still a new field. However, the government has realized its importance, and this sector has been identified to be one of the key economic drivers for the nation, contributing

to 5% of the nation's GDP by 2020. In achieving the objective, the National Biotechnology Division was formed under the Ministry of Science, Technology and Innovation (MOSTI), which has been given the responsibility to lead the national agenda through R&D, technology development, and promotion of biotechnology programs. Three interim laboratories were established—Genomic and Molecular Biology, Agrobiotechnology, and Pharmaceuticals and Nutraceuticals—to provide research infrastructure in the 8th Malaysia Plan. In 2011, the institutes were restructured and placed under an autonomous organization called the National Institutes of Biotechnology Malaysia (NIBM). While the three institutes focus on high-quality and market-driven R&D and innovations, NIBM's key role is to support and lead the commercialization of the R&D activities at the institutes based on industry requirements. NIBM was eventually registered in 2012 as a non-profitable company limited by guarantee under the purview of MOSTI.

Even though the support and infrastructure were under MOSTI, the regulation of biomedical products and clinical translation is under the jurisdiction of the Ministry of Health (MOH).

The MOH has identified human cell- and tissue-based products, including somatic cells (sometimes also referred to “tissue specific” or “adult”), engineered cells or tissues, stem cells, and cells derived from stem cells, which are

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intended for transfer into humans as Cell and Gene Therapy Products (CGTPs). All of these biological products will be regulated as medicinal products under the Sale of Drugs Act 1952: Control of Drugs and Cosmetic Regulations 1984 [P.U. (A) 223/84].⁷

These CGTPs are considered “engineered” if they have been subjected to substantial manipulation, to enhance their potential for regeneration and repair or replace tissue lost or damaged. Unfortunately, their unique source and manipulation make them difficult to assess in traditional regulatory systems. The variety of cellular products and potential applications are unlimited, and the ability of the regulatory body, that is, MOH to test them in a predictive manner, is limited and not cost-effective. While the existing regulation for biologics applies, CGTPs will require to be monitored from a different perspective and need continuous improvement.

Due to the complicated and continuous development of CGTPs, the MOH has divided the control and regulation of CGTPs into the following three main disciplinary approaches:

- The clinical use/medical procedure of the product will be under the ambit of Medical Practice of the MOH;
- The device element of such a product under the Medical Device Act provisions; and
- The National Pharmaceutical Control Bureau (NPCB) will ensure the product’s quality, efficacy, and safety.

The framework is based on a risk-management approach and it is designed to ensure public health and safety, while reducing the administrative burden and cost to the industry of the regulatory processes.

Stem cell research and therapy guidelines

In 2002, the MOH Malaysia formed a specific committee known as the Medical Research and Ethics Committee (MREC) to provide independent guidance, advice, and decision on ethical issues of health research or other specific protocols involving human subjects in a government institution. For a nongovernmental institution or private company, the committee may act as an independent ethics committee.⁸

Under the MREC, they form another specific committee that acts as an advisory in dealing with stem cell products and therapies. This committee known as the National Committee on Ethics of Stem Cells Research and Therapy (NCESRT), which comprises the National Stem Cell Committee, Obstetric & Gynecological Service Unit, and Pediatrics Services, formed a guideline published in 2009.⁹ Important points extracted from the guidelines include the following:

- (1) All stem cell research and applications must be reviewed by the respective institutional review board (IRB) and/or the institutional ethics committee (IEB) for approval. The IRB and IEC must strictly adhere to the National Guidelines for Stem Cell Research and Therapy.
- (2) The committee not only allows human adult stem cell research in general but also includes stem cells derived from fetal tissues from legally performed termination of pregnancy and embryonic stem cells

derived from surplus embryos. However, the committee only allows the manipulation and culturing of embryonic stem cells derived from the embryo formed not more than 14 days or before the formation of primitive streak, whichever occurs first.

- (3) Even though the guideline stated a strict requirement of the personnel in charge of the CTT research in which he or she must be adequately trained, proficient, and shall acquire privileging status from the respective institutions, it was not necessary to be a registered medical personnel.

In terms of therapy or clinical trial involving cell or tissue transplantation,

- (1) The committee that recognized the treatment using stem cell and tissue is still under the experimental setting. This clearly indicates that it should not be available as a commercial product.
- (2) Xenotransplantation shall not be performed and this includes human–animal chimeras breeding.

Healthcare institution laboratory for CTT must meet several requirements, which include the following:

- (1) Laboratories conducting stem cell research shall conform to required guidelines for good laboratory practices (GLP).
- (2) All laboratories conducting stem cell research for the purpose of clinical trials shall be GMP compliant as required by the NPCB.
- (3) Therapeutic outcomes, adverse effects, and tissue integration shall be documented or reported to the National Stem Cell Research and Ethics Subcommittee.
- (4) Private healthcare facilities and services intending to perform or performing stem cell or cell-based therapies shall be licensed under the Private Healthcare Facility and Services Act 1998.

In general, the guidelines served as a basis for all CTT research and clinical trials. In the point of time when these guidelines were written, CTT was still regarded as being in the experimental status and not for commercialization purposes.

Classification of cell and its manipulation

Although most of the research is done in government and private institutions, more private companies have emerged in providing research and marketing potential in CTT products. Following the guidelines of stem CTT, all institutions involved in clinical trials must have GMP facilities accredited by the NPCB. These regulatory guidelines are needed to safeguard public health in preventing transmission of diseases, contamination, and preserving functionality and assurance of clinical effectiveness and safety. However, since the hematopoietic stem cell has been used for cell transplantation to treat leukemia and similar diseases, it is illogical to consider it into the CTT product.

The risk-based approach to CTT regulation allows products that have a greater risk of adverse clinical outcome to require better control and, hence, more stringent regulations. Generally, two classes of products were suggested based on the risks defined as follows:

Minimal manipulation or nonsubstantial manipulation means the following:

FIG. 1. Summary of the pathways in construction of a Good Manufacturing Practice (GMP)-certified laboratory in Malaysia and the close relationship with research and development facilities.

- (1) For structural tissue, a process that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement;
- (2) For cells or nonstructural tissue, minimal manipulation means processing that does not alter the relevant biological characteristics of cells or tissues.

For products that require substantial manipulation, two classifications are identified as follows:

Class I: Lower risk cellular therapy products

A product eligible for regulation as Class I is not subjected to premarket review requirements or approval. The product must be registered and listed with NPCB to ensure that there is no risk for transmission of disease from the donor to recipient, avoid microbial contamination in process, and ensure the integrity and effectiveness of the products. The product is further regulated by

(i) site or facility licensure and listing; (ii) donor screening and testing; (iii) Good Tissue Practices (GTPs—21 CFR Part 1271); (iv) labeling; (v) adverse event reporting; and (vi) inspection and enforcement.

Class II: Higher risk cellular therapy products

If a cell therapy product does not meet all the four criteria defining minimally manipulated products, then the product will fall under Class II. The product is “highly processed,” used for other than normal function, are combined with non-tissue components, or are used for metabolic purposes” will be regulated as a biologic product. The product will be regulated using the Investigational New Drug (IND) framework and clinical trial pathway (that reports data from preclinical studies) and will require premarket registration, evaluation, and approval, which require sufficient data demonstrating that the product is safe and effective in humans. Both GTP and GMP are required.

In summary, all tissue engineering products and CTT products will be under the Class II classification.

Universiti Kebangsaan Malaysia, Tissue Engineering Center

Since the establishment of Tissue Engineering Center in year 2000, the regulations and guidelines of stem cell or any CTT have not been established in Malaysia. The Tissue Engineering Center at Universiti Kebangsaan Malaysia is one of the pioneers in human CTT culture and research. Our

FIG. 2. Overview of the process of a tissue engineering product and its quality control inspection.

Human resource: 1. Regular training and courses 2. Internal certification every 6 month 3. Aseptic training and retraining 4. Induction training for new staff	Instrumentation and environment: 1. Continuous environmental monitoring for each process 2. Cleaning for each process 3. Used test for new critical reagent 4. Schedule calibration
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FIG. 3. Regular training and inspection is important in maintaining the quality and reducing incidence. It can be divided into training the human resource and monitoring the environment and instruments.

milestone began with cartilage cell culture and the *in vivo* study in small animals.^{10,11} All studies have been submitted to the university's ethics committee before initiation. For animal studies, the university's animal ethics committee must approve the proposal separately.

In 2004, we began producing a human skin substitute, focusing on treating skin wounds.^{12–14} The prototype has been produced in 2008 using autologous fibrin as the bio-material to minimize controversy during submission to the ethics committee. It was produced inside the surgical operation room, which was adhered to be the most sterile environment in the hospital. Unfortunately, the ethics committee rejected the proposal as they required the cell and tissue products to be managed as per GMP-certified conditions. To complicate matters, there was no GMP laboratory in Malaysia available at that particular time. The nearest laboratory that has an experience in producing CTT with GMP compliance is in Australia. After lengthy discussion and agreement, we have chosen a consultant from Cell Therapies Pty Ltd,¹⁵ Melbourne, Australia, to build a GMP compliance laboratory in Malaysia. With the assistance and grants from Malaysia Technology Development Corporation (MTDC) and partly funded by the Universiti Kebangsaan Malaysia (UKM), the construction of clinical-grade GMP was initialized in the year 2010. The construction was completed in 2012. The total floor area is ~550 m² with three clean rooms of 25–36 m² in size. It is supported by unclassified laboratory area and general office and utility area. The entire area is being monitored with the Building Monitoring System (BMS) and Equipment Monitoring System (EMS). In July 2012, the laboratory was inspected by NPCB and had conformed to the requirement of GMP for CTT production for clinical trial.^{16–19} It took us almost 3 years, from the proposal to a complete accredited GMP laboratory, for cell and tissue engineering production, as summarized in Figure 1. It is also important to have a certified research and development laboratory for the continuity of CTT products. The big challenge is to translate the process of a CTT product from the research laboratory to a clinical product through the GMP facilities. To facilitate the process, the research and development laboratory must be certified as the ISO 9001 and ISO 17025. Running the GMP-certified laboratory needs a stringent quality control (QC) in every step of the process. In our laboratory, the QC is being applied in every transition of the process pathways (Fig. 2). This is to ensure that the quality of the product, maintenance of the environment, and handling process conform to the standard of procedure. The process of maintaining the GMP laboratory can be divided into two as follows: human resource and environmental and instrumentation. Our staff need continuous training in aseptic techniques, handling, and information on new products and processes. Further-

more, the facilities and instruments need strict monitoring and calibration (Fig. 3).

After receiving the GMP conformation certificate, our first objective was to perform a single-center, non-randomized, phase I clinical investigation of MyDerm™ as skin replacement in treatment of patients with diabetic ulcers, burns, and trauma injuries.^{20,21} Until today, the center is still running the clinical trials, which are expected to be completed by the end of 2015.

CTT companies in Malaysia

Cell and tissue engineering is still a new field in Malaysia. Regulation of CTT will be a major challenge for the National Regulatory Authority (NPCB) as too stringent and strict regulation will bring more harm to the development of the CTT product. A continuous discussion by the authorities and companies or institutions is needed to ensure a win-win solution. More companies are now aware of the regulations and an increase in the number of GMP laboratories is being inspected by NPCB for GMP certification based on the guidelines.²² To date, there are three other GMP-certified laboratories in Malaysia that deal with various stem cell therapy.^{23–25} Currently, there is no licensing scheme for companies producing CTT and they are given a letter of confirmation (LOC) with 3 years validity.

Conclusion

CTT is a new field in Malaysia, involving research and development in educational institutions. Given the complexities and many other emerging uncertainties, it is important for all stakeholders to work together to evolve a viable and pragmatic regulatory oversight framework and clinical utilization of CTT. It is now firmly established that all laboratories conducting clinical trial for CTT must be accredited and certified as GMP for CTT according to PIC guidelines. Due to the rapidly changing scientific knowledge, regulations for CGTPs are still evolving. At present, only a handful of laboratories have been accredited by NPCB for CTT, and the challenge is not only in building and certification but also in maintaining the laboratory in the long run. At present, Tissue Engineering Laboratory UKM is the only laboratory pioneering in clinical trials for the tissue-engineered product of skin substitutes known as MyDerm.

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