Provisional Translation (as of February 17, 2016)*

June 14, 2015

# Proposal on Basic Principle to Quality Assurance of Cell Therapy (CT) Products

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## 1. Introduction

The Pharmaceuticals and Medical Devices Agency (PMDA) Science Board has proposed the scientific and technical viewpoint on the operation of cell processing facility (CPF) for manufacturing cell therapy (CT) products to assure quality. The term CT products used in this document refer to cellular and tissue-based products including transgenic products and this proposal is not always applicable in gene therapy products such as vectors.

Since CT products are made of live cells derived from human cells or tissues, they have unique characteristics that are different from conventional medicine products and require specific control focused on their characteristics in manufacturing and quality control. As cells themselves provide the intended effectiveness and performance, CT products have diverse and complex quality attributes as well as a high level of heterogeneity. It is not easy to precisely understand these quality attributes by testing; furthermore, sufficient quantity of the product is frequently unavailable for examination on shelf life and for verification. Under these circumstances, there is a limit in performing verification as a batch release test; therefore, an approach different from the one for conventional

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biological products is required for designing the specifications for quality assurance of the product.

In addition, it is necessary to ensure viral safety and sterility. However, because the products themselves are composed of live cells, which are susceptive to heat and chemicals and are not suitable for filtration, it is beyond the level of currently available technology to design removal or inactivation process for viruses and microorganisms for CT products comparable to the level of conventional biological products. Accordingly, it will be important to develop a control strategy that specifically meets the product quality and its manufacturing process, conducted for the CPF.

Furthermore, the manufacturing process of CT products involves cultivation processes, which is mostly manually done. Therefore, it will be essential to achieve a constant quality for products batch to batch by thoroughly understanding the characteristics of the cells and their processing. Moreover, some procedures may require highly educated and trained personnel to manufacture the products with the intended properties. Although it is apparent that the product quality will be substantially affected by the education and training level of the personnel engaged in manufacturing control and quality control, the necessary education and training is currently not fully recognized.

Accordingly, the Science Board discussed the fundamental problems which occur by the operation of CPF regarding ensuring the quality of CT products. The principle of quality assurance is of particular importance. It is of the highest priority to establish the principle in working with CT products, which differ from conventional medicine products. The Science Board addressed its principle as a common basis of understanding for continuing further discussion. The Science Board summarized the approach toward system of manufacturing and quality control. It should be noted that the methods are different between investigational and post-marketing products. Furthermore, considering the scientific and technical limitation in quality assurance of CT products, the Science Board recognized the importance of quality risk management, knowledge management, training, and control strategy, the Science Board summarized the verification-based approach and its application method for quality assurance.

## 2. Principle

Quality control of medical products such as biological products, which are high molecular compounds with complex structure possessing a low level of homogeneity, is not considered to be done based entirely on specifications. Instead, the product quality is

verified by meeting properties defined in the specifications by (1) controlling variability in raw materials and during manufacturing process through in-process control, and intermediate product testing, and by (2)conducting characterization in advance to find the quality attributes and the range of variability of the product manufactured through the controlled manufacturing process. Variability in raw materials and manufacturing process are substantial in CT products, and furthermore, only limited information is available from characterization and specifications as to the complete quality attribute of the product. Under these circumstances, it is even more important to assure quality by focusing on monitoring deviations in intended quality through the manufacturing process controlling method, in-process control, and test on intermediates.

CT products have a higher level of heterogeneity than biological products along with complex and diverse quality attributes. Among these characteristics, the basic approach for defining intended characteristics of the product in quality specifications is still under discussion. However, the principle of the quality required for CT products is to achieve the efficacy and safety, by clinical trials. There is no difference in this fact considering the principle of any pharmaceuticals. Therefore, in defining quality specifications, it is necessary to identify the critical quality attributes, which are likely to be associated with its efficacy and safety, and to control the quality for which the consistency and equivalency are assured through non-clinical and clinical studies. Considering that only a limited number of tests could be conducted for the specification of the final CT product, it is essential to secure the consistency of the manufacturing process by accumulating knowledge on process parameters and in-process control associated with potential critical quality attributes throughout research and development, including the clinical study stage.

Regarding the manufacturing and quality control, compliance with relevant laws and regulations is apparent, and as a premise, intended product quality needs to be controlled for each batch of production. Although the quality control such as specifications and in-process control are developed during research and development, even more various types of deviations and variability will be found in the quality of the product because the actual manufacturing process involves a complex interaction between raw materials, manufacturing process, facilities, and other factors. It will, therefore, be important in the quality management to identify these variability during the manufacturing process and assess the quality risk from a scientific perspective.

Regarding the methodology of sterility assurance and concept of viral safety, direct application of the methodology in biological products will be difficult in most cases.

Therefore, in principle, the plan for ensuring sterility assurance and viral safety should consider the characteristics for each product evaluated as well as the properties of the facility for use in manufacturing (hardware) and the manufacturing procedures (software). In doing so, the effective approach will be to achieve the intended quality assured through total management, including raw material management, in-process control during the manufacturing process, test of intermediate and final products, and manufacturing control. Accordingly, it is effective to carry out comprehensive decision making by methods based on control strategy. Assurance of viral safety and sterility is a particularly critical element for CT products because biological materials derived from organisms are used in their production. However, it will be difficult to treat raw materials such as cells for sterilization prior to manufacturing or to include a sterilization process in the manufacturing process. Propagation of microorganisms is also a possibility if there is contamination during the manufacturing process. Similarly, it will not be easy to incorporate a viral inactivation process to the manufacturing process for adventitious viruses, including unknown species, and it is assumed that different species of viruses which contaminates the medium vary depending on the raw material. These issues make dealing with contamination risk pertaining to viruses and microorganisms an extremely critical issue in the manufacturing and quality control. Accordingly, sterility test by itself is not always satisfactory for sterility assurance from the perspective of its detection sensitivity. Furthermore, because of the possibility of selection or emergence of antibiotic resistant microorganisms, reliance on antibiotics with reluctance is not the appropriate method for sterility assurance that would give satisfactory reduction in quality risk. Moreover, careful and case-by-case consideration by referring to subsequent sections is required in dealing with the risk of viral safety that cannot be eliminated even by viral testing. In addition, with progress in new technological development pertaining to facilities, the conventional methodology may no longer be rational in some cases. Validation methods for assuring classification level required for sterile environment should be established with rationale from the viewpoint of the latest science and technology.

## 3. Quality system in manufacturing and quality control

Regarding manufacturing and quality control of marketed CT products, “Ministerial Ordinance on Standards for Good Manufacturing Practice of gene, cellular and tissue-based products” was already enforced as the regulation for Good Gene, Cellular and Tissue-based Products Manufacturing Practice (hereafter “GCTP Ordinance”). This ordinance was enforced separately from “Ministerial Ordinance on Standards for Good

Manufacturing Products for Drugs" (hereafter "GMP Ordinance") considering the uniqueness in quality control of CT products. Specifically, the ordinance describes the framework of quality assurance, and its principle is to construct a high level quality assurance system in addition to minimization of human errors such as prevention of, mix-up and deterioration in quality, as stated in the GMP Ordinance for medicine products. In application of GCTP, it is important to effectively construct quality system according to the GCTP Ordinance. Quality risk management and product quality review are extremely critical elements, in order to ensure that the quality system is functional as quality assurance. For this purpose, it is desirable to accumulate knowledge and utilize it for management.

Meanwhile, regarding manufacturing and quality control of investigational products, their adequate application is required by "Ministerial Ordinance on Standards for Good Clinical Practice of Gene, Cellular and Tissue-based products" (hereafter "GCP Ordinance"). However, to date, a specific method is not proposed. Similar to medicine products, research and development of CT products should include identification of critical quality attributes and critical process parameters, and development of control method along with recognition of quality risk. Therefore, for manufacturing and quality control during a development stage when manufacturing and testing methods have not been established, CT products generally share the same basic principle of good manufacturing practice (GMP) with any investigational drugs, including protection of patients in a study, assurance of the reliability of clinical studies, and ensuring the consistency and equivalency between investigational and post-marketing products. Because of this, the GCTP Ordinance, which is meant for post-marketing products, is unreasonable to apply investigation and CT products. Due to variability during manufacturing process and in raw materials, the validation can be insufficient to assure quality during the early stage of development. It is critical to ensure quality assurance by developing a flexible control strategy, which is scientific and based on the quality risk, for each stage of development. Verification and other methods should be appropriately utilized.

## 4. Quality risk management

The quality risk of CT products is not lower than that of biological products, and complete elimination of the quality risk is impossible by any means. Therefore, manufacturing and quality control should be used for its reduction. Recently, the importance of quality risk management in quality control of pharmaceuticals was proposed at the International

Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), of which the basic concept and methodology is presented in “Quality Risk Management” (hereafter “ICH guideline Q9”). Methods to quality risk management for pharmaceuticals can be applied to CT products, including evaluation of quality risk from the viewpoint of probability of risks causing health hazard or material defects, their severity, and detectability. Quality risk management should be applied to promote understanding in the product quality and manufacturing process. However, the scope of its application should be determined case-by-case considering the facilities (hardware), quality system (software), and development stage of the product. For example, maintenance of a facility suitable for cell processing requires appropriate environmental monitoring besides management of equipment by routine check. Furthermore, prevention of cross contamination requires the development of appropriate changeover procedures. These procedures should be developed with consideration of quality risk associated with the characteristics of the equipment, and further discussion should be made from the scientific and technical point of view. Regardless, in manufacturing and quality control, it is idealistic to take preventive measures rather than reacting after problems occur, by utilizing a systematic method involving quality risk assessment, control for mitigation or avoidance of the risk, and information sharing, surveillance, and review. Decision on whether to accept a quality risk should be made similarly as for pharmaceuticals for the fact that it should be based on scientific knowledge and result in the protection of patients.

## 5. Training, and knowledge management

CT products are manufactured through processing such as culture of autologous or allogeneic cells or tissues, and therefore, their manufacturing process is different from a series of automated and large-scale manufacturing processes conducted for pharmaceuticals. Most CT products are manufactured by manual work using aseptic technique in a restricted area such as a safety cabinet. Furthermore, since the final products are live cells, the conditions of cells can substantially change by the manufacturing process, and the product quality is affected by the technical skill and the degree of understanding of personals in manufacturing and quality control. Accordingly, it is extremely important to provide education and training to improve the skill of personals. Education and training on complicated manufacturing equipment such as isolators or flow cytometers should be provided for a deeper understanding of the structure and basic principle of the manufacturing equipment as well as the quality risk associated by the use of the equipment. Because a high level of technology is required for

cell characterization, knowledge sharing is difficult to achieve. Understandings in culture methods and the characteristics of the intended target cells or tissues should be obtained at the early stage of research and development, and it will be important to make standard operating procedures and plans/reports for transferring technology. In particular, managing, accumulating, and sharing information will not only provide the foundation for quality risk management in manufacturing and quality control but also lead to more effective education and training.

## 6. Control strategy considering product lifecycle

For CT products, in addition to assuring quality of the final products, another necessary approach is to achieve quality assurance by controlling the manufacturing process from upstream based on the knowledge of the product quality and manufacturing process. This type of approach is called a control strategy in the field of pharmaceuticals and its basic concept is described in “Pharmaceutical Quality System” (hereafter “ICH guideline Q10”). The control strategy is defined as a concept for consistently assuring the product quality and is different from assuring quality simply by specifications. It is explained as a controlling methodology that is systematically designed based on (1)understanding in primary design of the product quality and (2)manufacturing process and their quality risk management pertaining to controlling the manufacturing process from upstream to downstream and from the raw materials to the product to always obtain the intended results. In other words, it is a scheme which enables consistent achievement of the intended product quality by performing the manufacturing process exactly as planned. Although CT products are beyond the scope of ICH guideline Q10, it would be a more science-based approach to develop a control strategy using this concept as an appropriate methodology for quality assurance considering applicable test and the limit of detection sensitivity.

CT products are made of live cells, hence there are various factors causing variability and heterogeneity during manufacturing process and in quality attributes. Therefore, changes in manufacturing process after the late stage of clinical study is usually associated with a high development risk from the viewpoint of ensuring equality/equivalency of the quality. It is desirable to collect a broad range of information on quality from the early stage of development, and it is effective to make a plan based on knowledge management, quality risk management, and control strategy. In conducting a clinical study, it is recommended to establish a compatible quality assurance system with its best effort for protection of patients in the study even at an early stage of the clinical study. Furthermore, a framework

of conditional/ term-limited approval system, which is not the case for pharmaceuticals, has been established in the regulatory system for CT products, and hence, requirements during research and development and the post-marketing period may be considerably different from those of pharmaceuticals. Accordingly, research and development of CT products require a developmental strategy that takes into account of discrepancies in product lifecycle.

CT products are made of human-derived cells or tissues, and therefore, evaluation during the development stage may be under limited conditions from the viewpoint of availability. Therefore, pertaining to quality assurance of investigational products, it is expected that the control strategy using quality risk management be fully evaluated and developed in addition to understanding of manufacturing process and product characteristics based on as much information as possibly collected. Development of control strategy of investigational products is inevitable because the knowledge obtained from past experience, and the information obtained from pre-clinical study are extremely limited. Therefore, application of information obtained through production of investigational products to the control strategy of the investigational product in the next phase is important not only for quality assurance of the investigational products but also from the protection of recruited patients point of view. Although the knowledge from development stage for control strategy for the investigational product will be transferred onto post-marketing control strategy; however, it should be well understood that rationality and adequacy of the control strategy for post-marketing product are to be tested either by process validation or verification.

## 7. Verification

Validation and verification are extremely important elements in quality assurance. As a general rule, process validation is a requirement in application of manufacturing and quality control for post-marketing products. However, human cells or tissues are used as raw materials for CT products, and there may be restrictions on the availability of samples in advance, due to ethical aspects or difficulties in implementation owing to technical limitation. Verification can, therefore, be a method for ensuring quality.

While verification is confirmation of whether the intended results were obtained through manufacturing and quality control methods, it is more than a simple confirmation of the result of quality test. Process validation must be performed to make validation in advance in order for the products to be manufactured in a consistent manner, conforming to the

intended quality. However, in case of CT products with ethical restriction and technical limitation because of the use of human-derived cells or tissues, manufacturing and quality control methods should performed on the feasible level of validation that could be performed in advance.

Process validation is an activity for consistent quality assurance at a high level by identifying the factors associated with variability, such as the critical process parameters, and quality risks that contribute to the intended performance and quality of manufacturing process, and by controlling the manufacturing process through monitoring parameters and in-process control test. It is also a method for evaluating the planned control strategy in advance. On the other hand, verification is the confirmation and assurance of the product quality as intended for each batch, although not enough has been elucidated due to evaluation in restricted conditions or technical limitation. In other words, verification could be stated to be an approach taken with careful confirmation of in-process control in the upstream and quality attributes that may be critical for each batch of production. Furthermore, when verification is used for quality assurance, it should be noted that continuous verification following the verification plan is required even for post-marketing manufacturing.

From the quality assurance point of view, there is not much difference in the basic concept of verification of manufacturing of investigational products from that of the post-marketing products. However, because investigational products are manufactured at the development stage when the manufacturing methods and test methods are not finalized, the control strategy should be developed based on an attentive quality risk management system that is considering the knowledge available on product quality and manufacturing process at that time point.

## 8. Latest technology

Steady progress is being made in the development of technology involved in the CT products, including the development of advanced technology that could be the solutions to issues stated earlier. Rapid technological development is in progress, such as the automatic culture apparatus. There is a high possibility that an advance methodology for quality assurance will be established for ensuring sterility, by facility and environmental monitoring technology, not requiring reliance on sterility testing of the final products. It is also necessary to take a stance on incorporating new isolation and purification technologies such as the cell sorter. Taking account of such innovations, it is important to

understand that the methodology of quality assurance based on the current technology is just one approach, which is still in the course of development. It is strongly recommended to constantly review and improve the approaches and methods of quality assurance for CT products through actively incorporating the rapidly evolving new technologies.

## 9. Conclusion

The Science Board has held discussions on challenge in application of manufacturing and quality control of CT products and the basic concept for solution to the issues stated above. As a result, considering its dissimilarity from pharmaceuticals and the difference in the control methods between the development and post-marketing stages, the Science Board has summarized the basic concept for critical factors regarding the quality assurance of CT products and the basic approaches for achieving them.

Regarding CT products, issues in the manufacturing control and quality control such as, but not limited to, the methodology of sterility assurance are more diverse and complex as compared to those regarding conventional biological products. The Science Board also recognized once again that sterility and viral safety should be considered in raw material management of CT products even at a higher level than conventional biological products and that the available control methods are limited. Another issue is that a common consensus has not been achieved for the methodology and basic concept of manufacturing and product control during the investigational stage, although the GCTP Ordinance was promulgated and enforced as the standard for post-marketing manufacturing and quality control, and notifications and office memorandums regarding application of the ordinance are being summarized.

Especially, CT products are particularly of innovative field with limited experience in application to humans, and scientific knowledge and methods are in rapid progress. Regarding their research and development, investigation during research and development are performed in limited conditions due to restrictions in material availability since human-derived cells or tissues are used as raw materials,. Under such circumstances, development of common consensus in quality assurance, manufacturing control, and quality control of investigational products will not only help assuring safety of patients recruited in studies, promoting development, and facilitating marketing approval but also improve the quality of communication with the regulatory agency. Each CT product has diverse and complex qualities owing to the expected properties of the product. Therefore, it is needless to say that the decision should be made carefully for the

operation of quality control in the CPF. Consequently, the establishment of the basic concept and development of consensus as common knowledge is highly significant. Continuous efforts should be made in developing a comprehensive consensus through discussion based on the latest knowledge and collective wisdom from a scientific point of view.

The Science Board has held discussions on the CT products. The topics can possibly be applied as well to the assurance of quality consistency of test article provided for clinical research on CT products. Preparation of test article used in clinical research on regenerative medicine is subject to be controlled, following the Act on the Safety of Regenerative Medicine, which faced similar issues pertaining to its implementation. The basic concept can be an extremely effective methodology as solution for those issues, and therefore, it should be proactively applied for the operation of CPF for handling cells and tissues. However, the decision should be made with caution in a case-by-case examination for implementation in clinical research on regenerative medicine.