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Comparability assessment after changes in a mfg. process (1)

If the mfg. process is altered at some point during development, and if test results that were obtained using products manufactured before the change in mfg. method are to be used in the application for clinical-trial or regulatory approval, it is necessary to demonstrate that the products manufactured before and after the change in the mfg. process are comparable.

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Comparability assessment after changes in a mfg. process (2)

Subjects to Change:

- Cell substrates, other raw materials and manufacture-related substances (source, preparation methods and even type)
- Culture conditions
- Processing methods
- Formulation
- Storage and/or transportation methods

Criteria:

- Old Products *vs* New Products
- How to assess comparability in terms of Q/S/E

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Comparability assessment after changes in a mfg. process (3)

- Because there are a number of variations in the content, extent, and type of a comparability test of an individual product and in a specific case, it is difficult to devise technical guidance that is applicable to all situations.
- The design of comparability studies and evaluation of the results should be focused on the comparison of new products with old products in terms of safety, efficacy, or/and quality on a case-by-case basis.

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Establishing the storage and transport procedure for cells/ products at critical steps

If cells, an intermediate product, or a final product needs to be stored and transported, the storage procedure and duration, the containers for the transport, and the transportation procedure (e.g., temperature control) shall be set and their appropriateness explained.

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Preclinical Safety Testing of hCTPs (1)

- Relevant animal tests and/or in vitro tests may be performed to elucidate concerns about the safety of a hCTP when it is scientifically reasonable and technically possible.
- For non-cellular constituents and process-related impurities, safety concerns should be addressed as much as possible by physicochemical analyses, not animal testing.

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Preclinical Safety Testing of hCTPs (2)

- In the case of puluripotent stem cell derived products, the presence of undifferentiated cells in the final product and their potential to cause ectopic tissue formation, tumorigenicity, or malignant transformation are safety concerns.
  - To reduce the risk of contamination with such cells as much as possible via thorough analysis at the cell bank and/or at an intermediate-product stage or by developing and utilizing methods that effectively separate, remove, and/or inactivate these contaminating undifferentiated cells from the target cells during the mfg. process.
  - The administration route for the target cells may be selected to aid in the minimization of the safety risks.
  - It may be simple but useful to demonstrate that transformations other than those intended and abnormal proliferation of non-target cells have not occurred, for cells expanded beyond the limit set for routine cultivation.

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Preclinical Safety Testing of hCTPs (3)

- Animal testing of products of human origin does not always yield meaningful results. Thus, there may be a scientific rationale for preparing product models of animal origin and testing on appropriate experimental animals if more useful information may be obtained. In such a case, consider conducting tests on suitable animal models for each target disease.
  - However, because the use of identical procedures in nonhuman animals will not necessarily yield cell groups that possess characteristics identical to those of cells that constitute a hCTP and because a product of animal cell origin that was manufactured using identical processing, including culture conditions, will not necessarily be comparable to a hCTP, careful feasibility studies are required beforehand when adopting, conducting, and evaluating such studies. When conducting animal experiments using an animal model product obtained from nonhuman animal species, explain the suitability of the extrapolation.

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Preclinical Safety Testing of hCTPs (4)

- Depending on the case, consider test systems that employ cells and clearly explain the appropriateness of the test system when conducting tests using this kind of approach.
- Conduct necessary and appropriate tests, taking into account the characteristics of the product and intended clinical use and evaluate and discuss the results in a comprehensive manner.

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Preclinical Safety Testing of hCTPs (5)

- Compliance with GLP requirements may not be possible or feasible for some toxicology assessments. However, toxicology nonclinical studies should be in substantial compliance with GLP and deviations should be described and justified.
- The principles of Reduction, Refinement, and Replacement of Animal Use (the "3Rs") should be considered during the development of a nonclinical program for a hCTP.

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Nonclinical Studies Supporting the Potency or Efficacy of hCTPs

- A well-designed study using experimental animals and/or cells should be performed in order to demonstrate the functional expression, sustainability of an effect, and/or anticipated clinical efficacy (POC) of a hCTP to the scientifically reasonable and technically possible extent.
- For transgenic cells, demonstrate expression efficiency, sustainability of expression, and biological activity of desired products of the (trans)gene and discuss the feasibility of the anticipated clinical efficacy (POC) of the hCTP in question.
- Where appropriate models of products derived from processing of animal cells and/or animal models of a disease are available, use them to study the potential therapeutic efficacy of the product.

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Pharmacokinetics/Biodistribution of hCTPs (1)

Pharmacokinetic studies of the internal behavior of cells/tissues that constitute the final products or expression products of transgenes, (these studies may include absorption and distribution in experimental animals), should be performed to the technically possible and scientifically reasonable extent.

➢ These studies are expected to estimate the survival of cells/tissues administered to patients and the duration of their effects and to determine whether the intended efficacy is successfully achieved.

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Pharmacokinetics/Biodistribution of hCTPs (2)

- Clarify, using animal studies, the rationale for the administration method for the hCTPs.
- It is assumed that local administration is preferable to systemic administration.
  - ➢ However, if the benefits to patients can be explained in a rational manner, it is acceptable to use systemic administration.
- An administration method that minimizes distribution of a hCTP to organs other than the target organ is preferred.
- When the cells or tissues are directly applied or alternatively targeted to a specified site where they can be expected to perform their actions, clarify the localization, and discuss the effect of the localization on the efficacy and safety of the product.

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Clinical Trials (1)

- An investigational clinical trials can initiate after determination that there has been no quality or safety problems exist that might pose an obstacle to initiation of human clinical trials, taking into consideration the product's usefulness with reference to the study design.
- It is also important to entrust the patient with the right to make a decision after receiving all of the available information, including all information on presumed risks and anticipated potential benefits.

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Clinical Trials (2)

- Clinical trials should have an appropriate study design and specified endpoints. They should be designed based on the desired cells/tissues, target disease, and method of application.
  - Target disease
  - Target subjects and patients who should be excluded as participants
  - Details of the therapy to be performed on the subjects, including the application of hCTPs and drugs used concomitantly, if any.
  - Appropriateness of conducting the clinical trials in light of existing therapeutic methods
  - Plan for explaining the clinical trial to the patients, including the currently known risks and benefits of the product

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Clinical Trials (3)

- For early-phase clinical trials, especially first-in-human trials, the primary objective should be an evaluation of safety.
- The trial objectives may focus on characterizing the safety profile of the feasible dose or doses, rather than finding the maximum tolerated dose (MTD).
- A common secondary objective is to obtain preliminary assessments of product activity, using either short-term responses or longer-term outcomes that could suggest a potential for efficacy.
- Choice of the subjects to include in the trial depends on the expected risks and potential benefits, recognizing that there will be considerable uncertainty about those expectations in an early-phase trial.

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Clinical use after marketing authorization

At the stage of clinical use after marketing authorization, major points to consider may include:
1) Quality control and maintaining consistency of the products intended for clinical use by means of specifications and good mfg. practices and
2) Postmarketing surveillance

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Monitoring and Follow-up (1)

- In addition to general tests and monitoring to look for unanticipated safety issues, evaluations might include acute or delayed infusion reactions, immune response to the product, autoimmunity, graft failure, GVHD, new malignancies, transmission of infectious agents from a donor, and viral reactivation.
- Attempts should be made to determine the duration of persistence of the product and its activity. The potential for migration from the target site, ectopic tissue formation, or other abnormal cell activity should be addressed.

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Monitoring and Follow-up (2)

- In general, the duration of monitoring for adverse events should be designed to cover the time during which the product might reasonably be thought to present safety concerns.
- The appropriate duration of follow-up depends on the results of preclinical studies, experience with related products, knowledge of the disease process, and other scientific information.

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- In this presentation, the concept and scientific elements of a minimum consensus package plus the case by case approach for hCTPs for product development, evaluation, and control have been overviewed.
- Subsequent sessions (Sessions 3-6) will address in detail: 1) specific points to consider for the evaluation and control of hCTPs that are different from those of traditional biological/biotechnological protein products; and 2) identification of specific point/issues for a specific type of product, as well as very critical points/issues for various types of products.

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The overall concept is that cell therapy can be advanced efficiently, effectively and reasonably through the use of such a "Minimum Consensus Package" + "Add-on Package" in an individual case.