

# Outline of the Law for Partial Revision of the Pharmaceutical Affairs Law (Act No.84 of 2013)

In order to ensure the safe and swift provision of pharmaceuticals, medical devices, etc., necessary measures are taken including establishment of the obligation to notify package inserts, expansion of the range of certification of medical devices by Accredited Certification Bodies, and establishment of a conditional and a term-limited approval system for regenerative medical products.

## I Outline of the Act

### 1 Enhancement of safety measures pertaining to pharmaceuticals, medical devices, etc.

- (1) Implementation of regulations necessary for prevention of outbreak and expansion of health and hygiene hazards is clearly specified in the aim of the Pharmaceutical Affairs Law.
- (2) Responsibility pertaining to the assurance, etc., of the quality, efficacy and safety of pharmaceuticals etc. is imposed on relevant parties.
- (3) Marketers of pharmaceuticals etc. are to prepare package inserts based on the latest findings and notify them to the Minister of Health, Labour and Welfare.

### 2 Establishment of regulations based on the characteristics of medical devices

- (1) Marketing and manufacturing of medical devices are stipulated in a chapter separated from the chapter for pharmaceuticals etc.
- (2) The certification system of medical devices by private third-party bodies is extended to specially controlled medical devices with stipulating the standards.
- (3) Stand-alone programs used for diagnosis etc. are to be subject to approval, certification, etc. of marketing, as medical decides.
- (4) Regarding the manufacturing of medical devices, the current license system is simplified to a registration system.
- (5) Standard conformity inspection for manufacturing control and quality control methods of medical devices is rationalized.

### 3 Establishment of regulations based on the characteristics of regenerative medical products

- (1) “Regenerative medical products” are newly defined, and regulations on safety measures etc. are to be established based on their characteristics.
- (2) Regarding non-uniform regenerative medical products, it will be made possible to give conditional and term-limited marketing approval specifically early if the efficacy can be assumed and the safety is confirmed.

### 4 Others

The title of the Pharmaceutical Affairs Law is revised to the “The Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices.”

## II Implementation date

November 25, 2014 (promulgated on November 27, 2013)

# 1. Enhancement of safety measures pertaining to pharmaceuticals, medical devices, etc.

## Revision Background

- Promotion of practical application of pharmaceuticals and medical devices requires simultaneous enhancement of safety measures.
- Package inserts attached to pharmaceuticals and medical devices are important to inform the medical sites of the precautions etc., and the necessity to review the placement of package inserts was pointed out during the investigation on the hepatitis infection case. Additionally, while it is important that the latest findings are reflected on package inserts, the current Pharmaceutical Affairs Law does not clearly specify that point.
- Therefore, it is necessary to enhance the safety measures pertaining to pharmaceuticals, medical devices, etc. by reviewing the placement, etc., of package inserts.

## [Review of the placement of package inserts]

- (1) Marketers of medical devices shall prepare package inserts based on the latest findings, and notify them to the Minister of Health, Labour and Welfare. In addition, from the viewpoint of swift information provision, the notified package inserts shall be immediately published online.

## [Other amendments]

- (2) Implementation of regulations necessary for prevention of outbreak and expansion of health and hygiene hazards is clearly specified in the aim of the Pharmaceutical Affairs Law.
- (3) Roles of relevant parties (e.g., relevant business operators, medical workers) for the purpose of assurance, etc., of the quality, efficacy and safety of pharmaceuticals etc. are clarified.
- (4) The notification destination of side effects etc. by medical institutions is integrated to the notification destination of marketers, i.e. the Pharmaceuticals and Medical Devices Agency (PMDA). The Japanese government may order PMDA to carry out arrangement of information, and is to take post-marketing safety measures.

## 2. Establishment of regulations based on the characteristics of medical devices

### Revision Background

- Medical devices have characteristics different from pharmaceuticals (\*), where products improved and modified in short cycles are supplied to the market, in many cases, similar to mechanical products like personal computers, for instance.
- While development and practical application of new medical devices is expected to contribute to improving the quality of medical services and as an industrial field that leads the economic growth of Japan, there have been issues pointed out (e.g., a long period of time is required for approval and marketing).
- Further, promotion of international expansion of medical devices requires considerations on conformity to international rules.
- Therefore, it is necessary to achieve swift application of medical devices and rationalization of regulations through regulatory reform based on the characteristics of medical devices.

#### \* Main characteristics of medical devices

- (1) Products are practically applied after going through actual use at clinical sites.
- (2) Modification and improvement are constantly made, and the lifetime per product is short.
- (3) Efficacy and safety largely rely on the skill of physician etc., and various products are used in small quantities at clinical sites.

### **[A new chapter separate from pharmaceuticals is created, medical devices clearly shown in the name of the Law]**

- (1) Marketing and manufacturing of medical devices is stipulated in a chapter separated from the chapter for pharmaceuticals.
- (2) “Medical devices” is clearly shown in the name of the “Pharmaceutical Affairs Law”.
  - The name after revision shall be the “The Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical.”

### **[Simplification of regulations and systems for swift practical application]**

- (3) The certification system of medical devices by private third-party organizations is extended to specially controlled medical devices with stipulating the standards, to achieve prioritization and expediting of PDMA's investigation on new medical devices.  
(Examples) Blood filter for heparin-coated cardiopulmonary bypass circuit, pen-type insulin injector

- \* Additionally, necessary regulatory arrangement in accordance with the expansion of the certification system is made, including succession of the position of those received marketing certificate, approval of operational rules for Accredited Certification Bodies, and an order of certification cancellation etc. by the Minister of Health, Labour and Welfare.

## **[Clarification of the placement of stand-alone programs]**

- (4) Taking into account their placement as medical devices in Europe and the US, stand-alone programs are to be included in the range of medical devices subject to marketing etc.  
(Example) Programs for processing, storing, displaying, etc. of image data taken by MRI etc.

## **[Other revisions]**

- (5) Regarding the manufacturing of medical devices, the current licensing/approval system is revised to a registration system, and requirements are to be simplified.
- (6) Regarding approval and certification, QMS inspection (inspection on the conformity of manufacturing control and quality control to standards) is rationalized and carried out for the product groups (roughly categorized by the characteristics etc. of medical devices) instead of individual products.
- \* Products in the same product group of a product that has already passed QMS inspection in principle exempt from QMS investigation.  
QMS inspection by Prefecture is abolished; QMS inspection is carried out by certification bodies and PMDA.
- (7) In place of the current re-investigation and re-assessment, regarding medical devices designated by the Minister of Health, Labour and Welfare (\*), their efficacy and safety are to be checked by investigating the treatment outcome within a period that is specified in accordance with the characteristics of the device.
- \* Assumes products that are left inside human bodies for a long period of time, such as mechanical hearts
- (8) Renting of specially controlled medical devices will be subject to licensing or notification, even when the renting does not involve obtainment of the value.
- (9) When selling medical devices to medical institutions etc., inclusion of package inserts may be omitted if certain conditions are met, including online publication of information and consent given by the medical institution.

### **3. Establishment of regulations based on the characteristics of regenerative medical products**

#### **Revision Background**

- Regenerative medicine using iPS cells etc. receives high expectation from the nation towards practical application as ground-breaking medicine. Meanwhile, there are concerns over its safety etc.
- To that end, for regenerative medical products, it will be necessary to establish a system etc. based on their characteristics(\*) to achieve swift practical application while ensuring their safety.

\* Main characteristics of regenerative medical products

The quality is non-uniform since they use human cells etc. and thus reflect individual differences.

#### **[Definition separated from pharmaceuticals and medical devices]**

- (1) “Regenerative medical products” are newly defined separately from pharmaceuticals and medical devices, and a “Chapter” for regenerative medical products is created.

<Range of regenerative medical products>

- Processed (e.g., cultured) human cells that are used for the purpose of (1) reconstruction, repair or formation of human body structure or function or (2) treatment or prevention of disease, or
- Those that are used by introducing into human cells for the purpose of gene therapy
  - \* These products have the characteristics where the quality is non-uniform since they use human cells etc. and thus it is difficult to predict the efficacy. The range is specified by a Cabinet Order.

#### **[Introduction of conditional and term-limited approval system]**

- (2) Regarding non-uniform regenerative medical products, a system that allows for early approval with conditional and term-limited licensing is introduced if the efficacy can be assumed and the safety is confirmed. In that case, the efficacy and safety are to be again investigated after licensing.

- \* Assumes a condition for limiting the sale destinations to medical institutions etc. that have specialized physicians and equipment and a period within a range of no more than 7 years in principle, respectively, for the condition and term. Additionally, approved entities are required to re-apply for approval with providing additional material etc. on the treatment outcome within the term.

### **[Arrangement of safety measures etc.]**

- (3) Physicians etc. shall strive to provide patients with appropriate explanations and to obtain consent from the patient on the use of products.
- (4) Post-marketing safety measures are to be taken, including investigation on the treatment outcome, periodic reporting on infectious diseases, and recording and storing of information on the patients to whom the product was used.
  - \* Regarding regenerative medical products designated by the Minister of Health, Labour and Welfare, marketers are to store records for a long period of time, and medical institutions are to record and store information on the patients to whom the product was used.
- (5) Health hazards originating from regenerative medical products are to be covered by the Relief Systems for Adverse Drug Reactions and Infections Acquired through Biological Products.

### **[Other revisions]**

- (6) Standards of manufacturing control and quality control in manufacturing sites are established in order to ensure the quality, safety, etc.
- (7) While collection of blood from human bodies on a regular basis is prohibited in principle, for regenerative medical products, it will be made possible to manufacture products by using blood collected from human bodies by the manufacturer or a medical institution. (\* Revision of the Law on Securing a Stable Supply of Safe Blood Products)

## **4. Implementation date**

November 25, 2014 (promulgated on November 27, 2013)

# Introduction of Package Insert Notification System

Package inserts are...

- Documents that describe precautions etc. of pharmaceuticals etc. in order to notify the users of necessary information.
- Created by each marketer based on the description guidelines (Notification), and revised as necessary based on safety information including reports on side effects.

“Review of Pharmaceutical Policies etc. for Prevention of Recurrence of Adverse Drug Reaction (First Proposal)”  
(April 30, 2009)

Commission on Investigation of the Hepatitis Infection Case and Ideal Pharmaceutical Policies for Recurrence Prevention

It was pointed out that package inserts shall be regarded as official documents and the governmental responsibility shall be clarified, referencing the systems in Europe and the US, by reviewing their placement on approval (e.g., changing them to be subject to approval).



“Summary on Regulatory Reform Including Pharmaceutical Affairs Law”  
(January 24, 2011)

Health Science Council Study Group on Regulatory Reform for Pharmaceuticals etc.

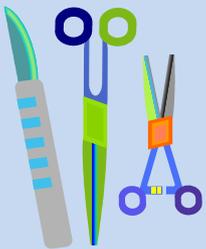
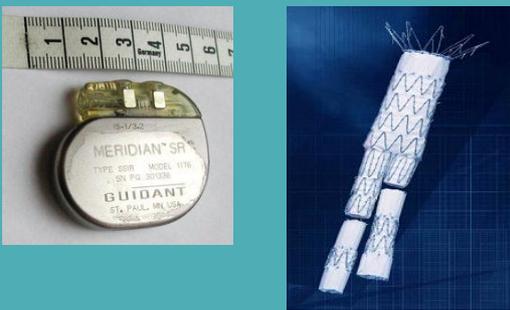
- Regarding the placement of package inserts, taking into account their importance, it was deemed necessary to clarify the national government’s regulatory authority under the Pharmaceutical Affairs Act, and discussions were held on the method whether it will be subject to certification or obligation of notification will be imposed on companies.
- During the discussion, there were concerns raised on the potential withering at medical sites if they are made subject to certification, and the opinions predominantly recommended revision of the system to impose obligation on marketers to notify the package inserts in advance before commencement of marketing and at the time of revisions made.



**Based on the summary, a package insert notification system is introduced**

# Classification and Regulations of Medical Devices

Low ← Risk → High

International classification*1	Class I	Class II	Class III	Class IV
Examples	<p>Those considered to <u>have extremely low risk to the human body</u> even when a failure occurs</p> <p>(Examples) External diagnosis devices, steel instruments (e.g., scalpel, tweezers), X-ray films, items for dental techniques</p> 	<p>Those considered to <u>have relatively low risk to the human body</u> even when a failure occurs</p> <p>(Examples) MRI equipment, electronic endoscopy, catheter for digestive organs, ultrasonic diagnostic equipment, dental alloys</p> 	<p>Those considered to <u>have relatively high risk to the human body</u> when a failure occurs</p> <p>(Examples) Dialyzer, artificial bone, artificial respirator</p> 	<p>Those that are highly invasive to the patient and <u>potentially have a direct impact on human life</u> when a failure occurs</p> <p>(Example) Pace maker, artificial heart valve, stent graft</p> 
	Classification by PAA	General medical devices	Controlled medical devices	Specially controlled medical devices
Regulation	Notification	Certification by a third party*2	<p>Extended by the revision</p> <p>Certification by the Minister (investigation by PMDA)</p>	

\*1 Pharmaceutical Affairs Law (PAA) adopts the concept of 4 risk-dependent classification categories that were agreed upon in December 2003 by the "Global Harmonization Task Force on Medical Devices (GHTF)" in which Japan, the US, Europe, Australia and Canada participated.

\*2 A system for private third-party certification bodies accredited by the Minister of Health, Labour and Welfare (currently 12 organizations) to certify the conformity of products to the standards specified by the Minister, for the purpose of eliminating the necessity to obtain an approval from the Minister.

# Stand-alone Program

## Stand-alone program

Programs\* that exert functions as medical devices by being installed into a general PC etc.

\*Program: A series of orders given to computers to obtain certain results

Medical devices that use programs under the current Pharmaceutical Affairs Law

## Image Analysis Workstation

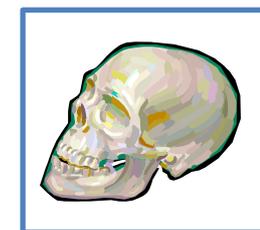


<Use example>



CT data

3D image processing by a program installed in the product



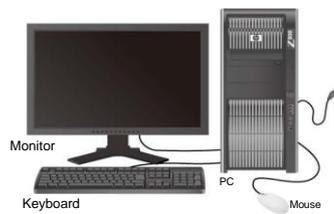
3D image of the skull

Used for processing, storing, displaying, etc. of image data obtained by X-ray CT, MRI, PET-CT, etc.

Current PAA



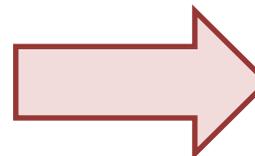
Software component (program)



Hardware component

A Software component alone is not covered by PAA, and is regulated in the form of being installed into the hardware.

Revision



Stand-alone program



Software component (Program)

**Programs themselves are covered by PAA**

\* They are already regarded as medical devices in Europe and the US

# Regenerative Medicine

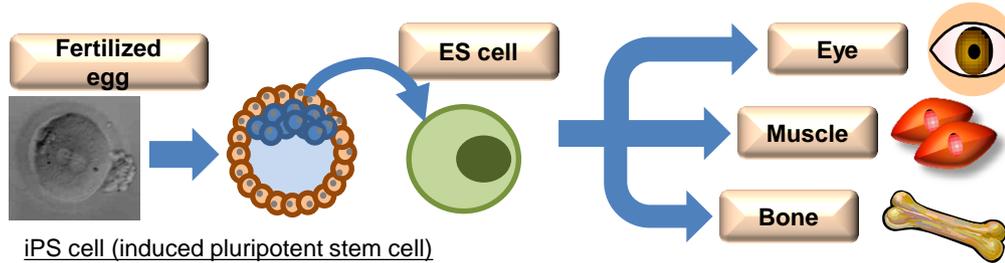
- Regenerative medicine is medicine to regenerate tissues and organs whose function became inadequate due to illness or injury, and expectation is placed on application of regenerative medical technology to drug development.

## Regenerative medicine

### [Medicine]

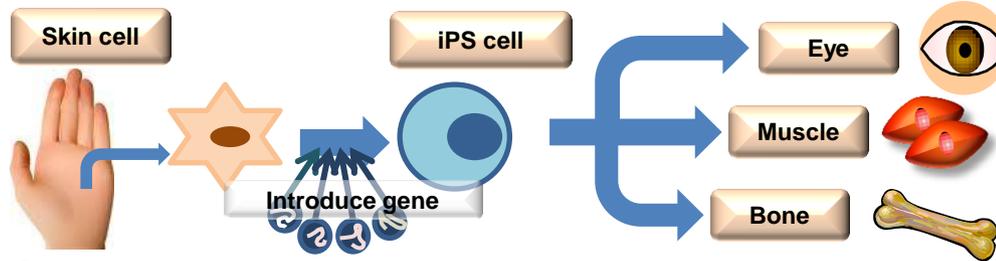
- ES cell (embryonic stem cell)

Cells created from fertilized eggs. There is an ethical issue.



- iPS cell (induced pluripotent stem cell)

Cells created by introducing specific gene to somatic cells. There are issues of malignant transformation, etc.



- Somatic stem cell

Cells originally possessed by organisms. Differentiate into limited types of cells.

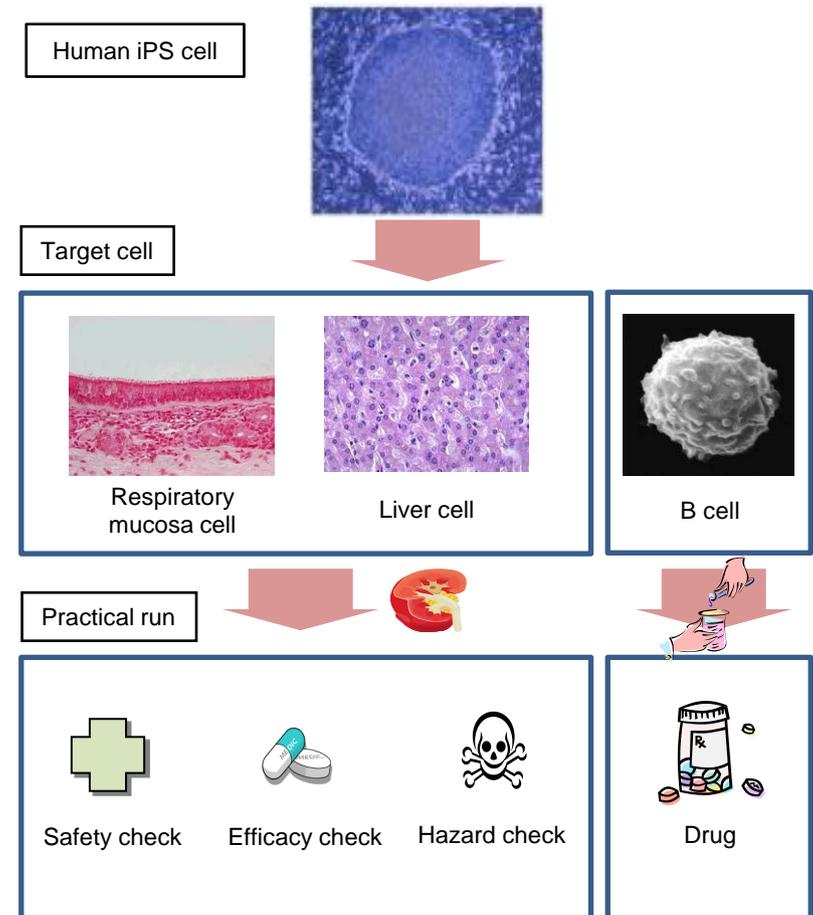


- Somatic cell other than somatic stem cell

Cells originally possessed by organisms. Differentiated into specific types of cells, and do not become any other cells.

### [Drug development]

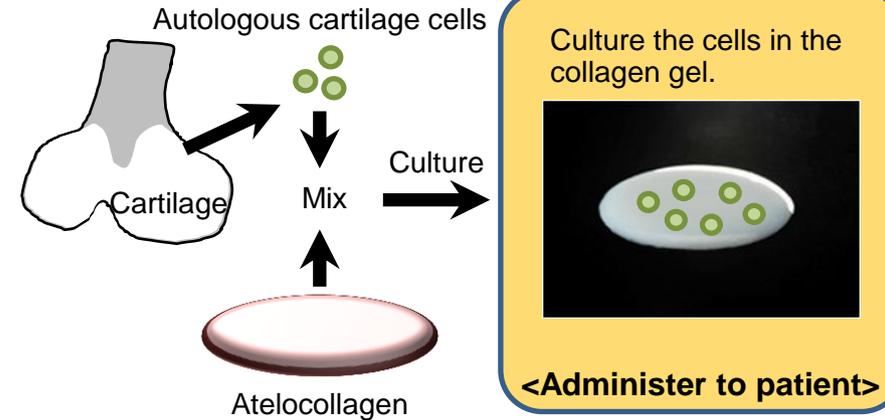
- The safety etc. of drug is confirmed by creating the target human cells from human iPS cells etc.



# Examples of Regenerative Medical Devices

[Example of reconstructing a body structure using cells: Cartilage regeneration product]

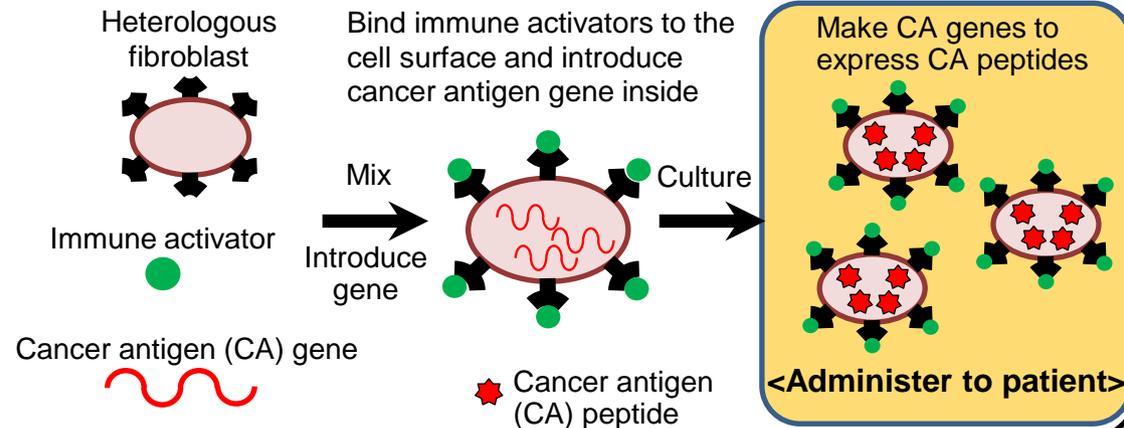
Products where autologous cartilage cells are cultured in an *in vitro* collagen gel. Recovery of the cartilage function is anticipated by transplanting the product to the cartilage damaged by injury etc. and producing cartilage-like tissues consisting of cartilage cell – collagen gel etc.



[Example of treating disease using cells: Cancer immunity product]

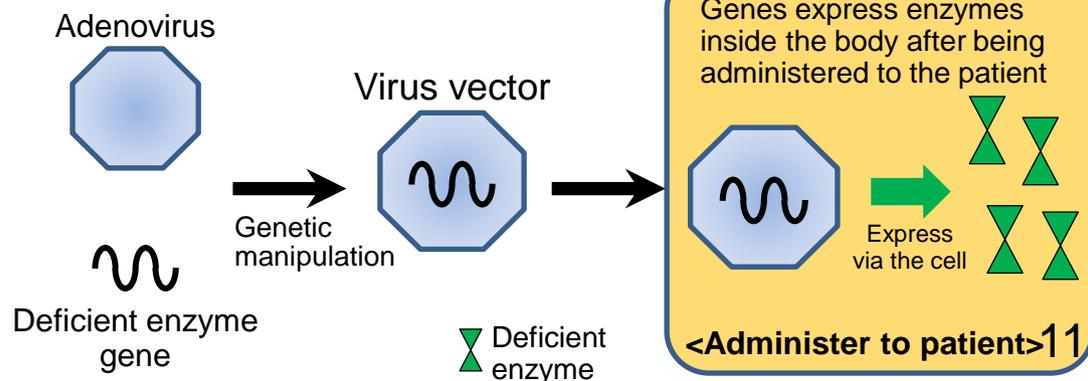
Therapeutic effects on cancer are anticipated by enhancing the cancer immunity function of the body using cells that contain immunocyte-activating substances and cancer antigen peptides.

\* Gene introduction is also carried out for this product.



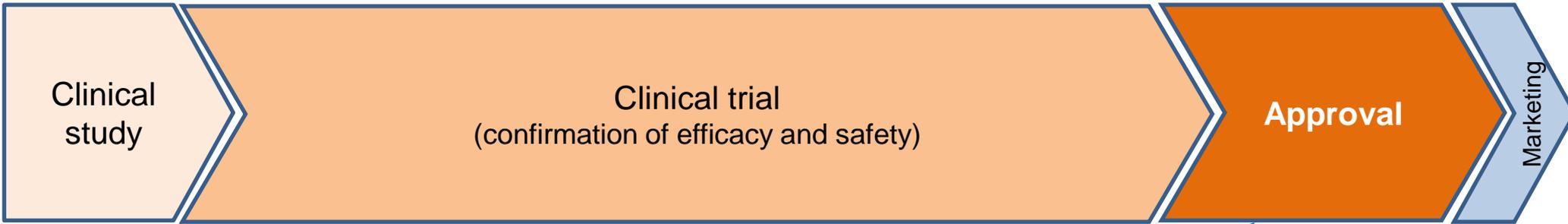
[Example of gene therapy: Hereditary disease treatment product]

Therapeutic effects on hereditary disease are anticipated through administration of viruses retaining congenitally deficient genes (e.g. adenosine deaminase gene) and expression of the introduced genes.



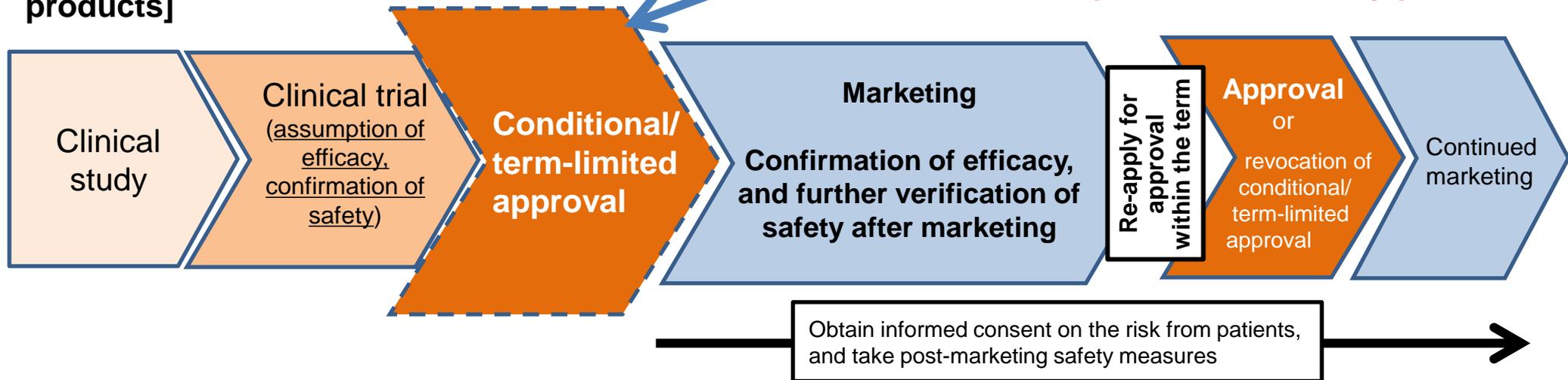
# Approval System that Accommodates Practical Application of Regenerative Medical Products (conditional and term-limited approval)

## [Conventional approval process]



<Problem in applying conventional approval system to regenerative medical products>  
Data gathering and assessment for the purpose of checking the efficacy requires a long time due to the non-uniform quality reflecting the individual differences since human cells are used.

## [Approval system that accommodates early practical application of regenerative medical products]



- **Efficacy is assumed in a short period of time** compared to the conventional method, from a certain number of limited cases.
- Regarding the safety, side effects etc. in the acute phase can be assessed in a short period of time.