Biological Products Regulation in Japan

-Cancer Vaccines and Immunotherapy-

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(PMDA)

Today's Topic

- Outline of PMDA
- Japanese approval process for pharmaceuticals
- Japanese regulation of biological products
- Japanese regulation of Gene-therapy or Cell / Tissue-based Products
- Development of biological products used in cancer treatment

Outline of PMDA

Introduction of PMDA

- NAME: Pharmaceuticals and Medical Devices Agency
- Date of Establishment : April 2004

Established as an Incorporated Administrative Agency (IAA) in April, 2004 by integrating 3 review-related organizations.

- Effective operation under “Medium Term Plan” for 5 years’ activities (04’-08’)
- PMDA submits performance report to MHLW annually, and that is evaluated by the “IAA Evaluation Committee” for necessary improvement

Our Mission

To Ensure **Faster** Access to
More Effective and **Safer**
Pharmaceuticals & Medical Devices
for the Public

Improving Public Health

3 major work areas

Review and Audit for Drugs/ Medical Devices

- Clinical Trial, etc Consultation
- Review of Efficacy and Safety
- Conformity Audit for Application Materials of GLP,GCP and GMP

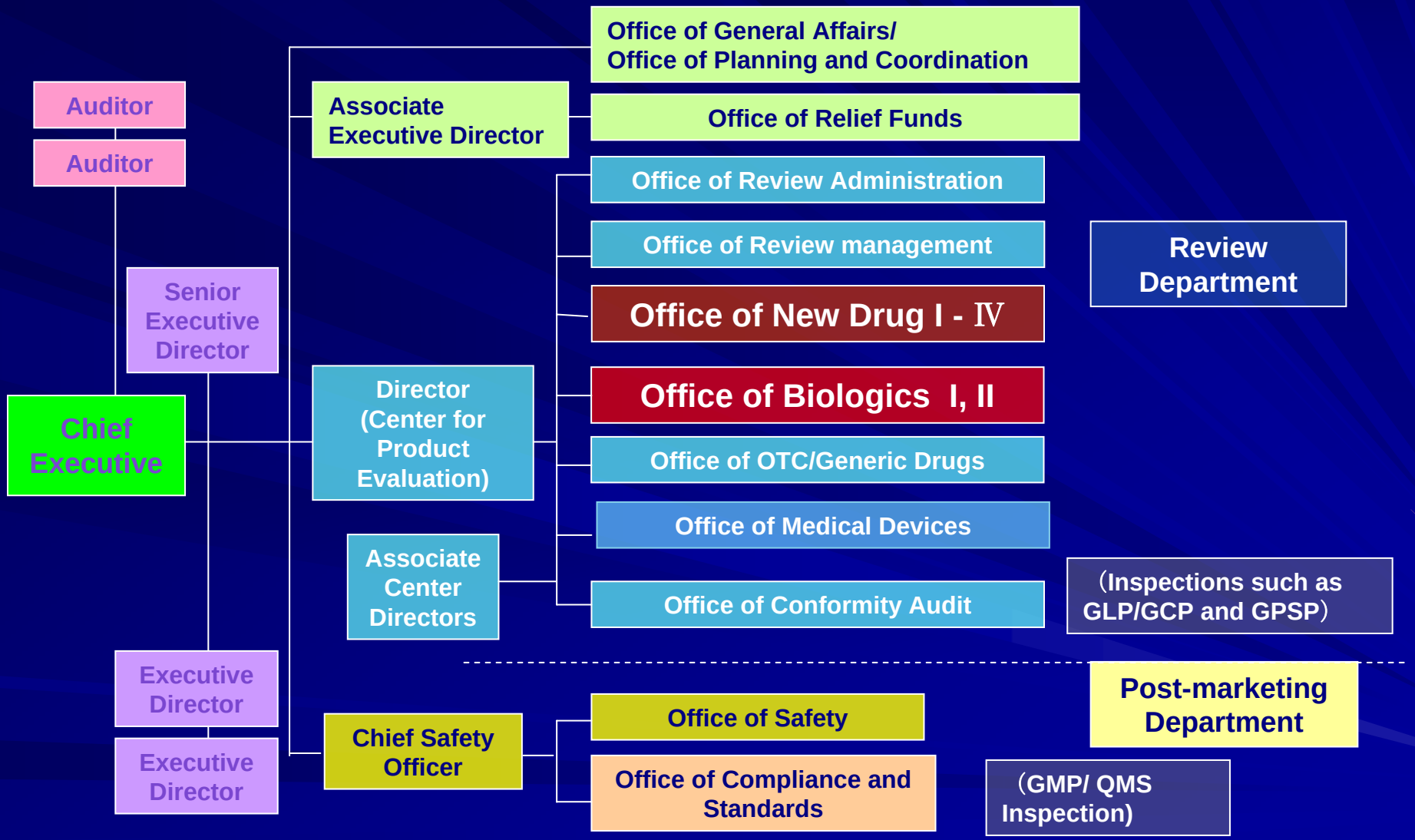
Post-marketing **Safety** Operations for Drugs/ Medical Devices

- Reinforced Safety Information (Database)
- Scientific Review and Research for Safety Information
- Provision of Information (via the Internet), Telephone Consultation Services for Consumers

Relief Service for ADR and Other Infectious Disease

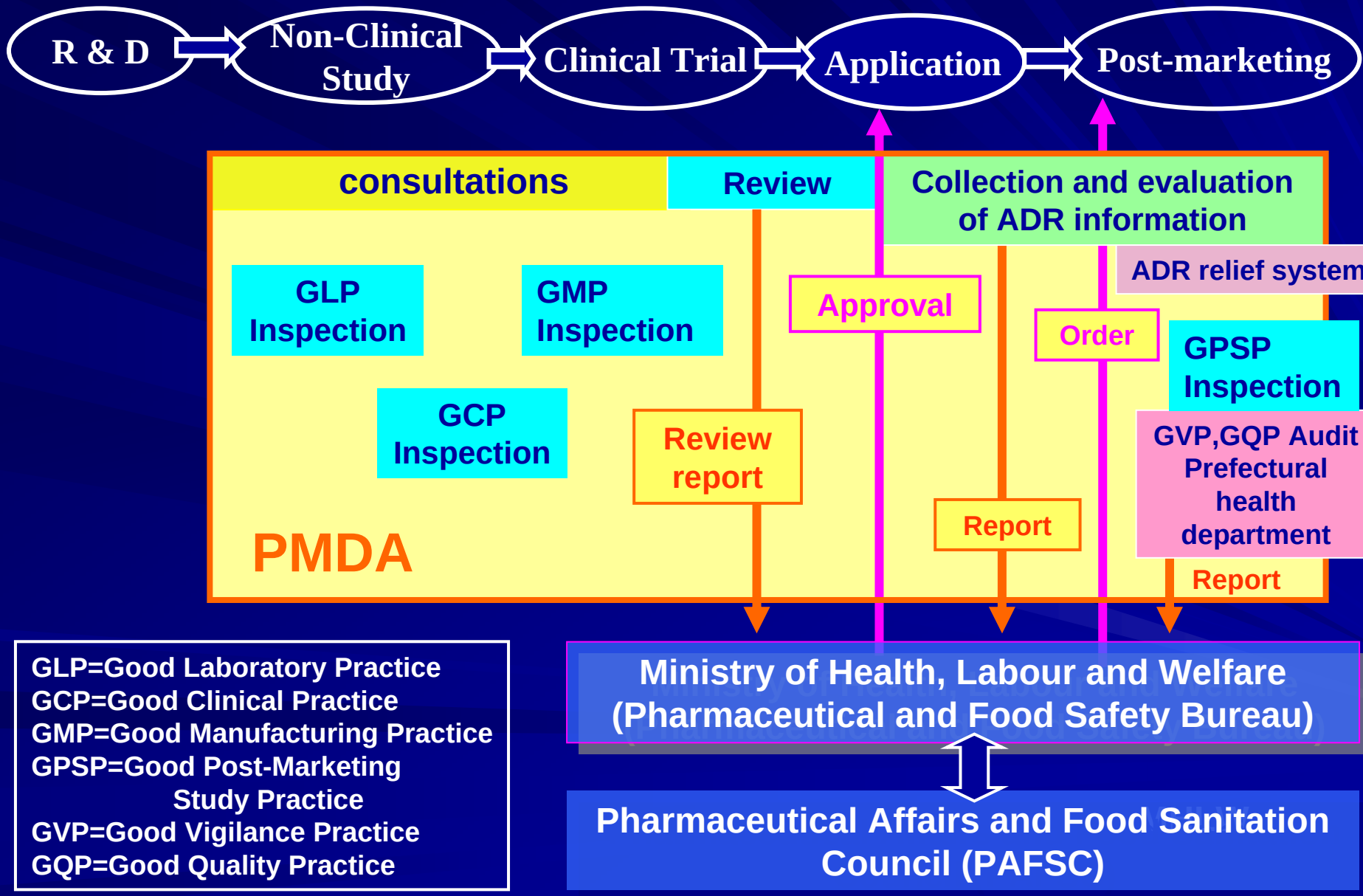
- Provision of Medical Expenses, Disability Pensions etc.
- Relief Service for SMON, HIV-positive and AIDS patients, and HCV-positive and HC patients

Organization Chart of PMDA



Number of staff: 426(‘08) with approx. 900 external experts

Work flow of Review



GLP=Good Laboratory Practice
GCP=Good Clinical Practice
GMP=Good Manufacturing Practice
GPSP=Good Post-Marketing Study Practice
GVP=Good Vigilance Practice
GQP=Good Quality Practice

- Japanese approval process for pharmaceuticals

Flow of marketing approval for pharmaceuticals and medical devices: form development to marketing (Patients)

Research and development

Non-clinical test

Clinical trials

Approval application

Approval

Approval

consultation
(Face-to-face advice)

Review

Post-marketing safety measures

Adverse health effect relief

Non-clinical tests
・Animal test

Phase I trials

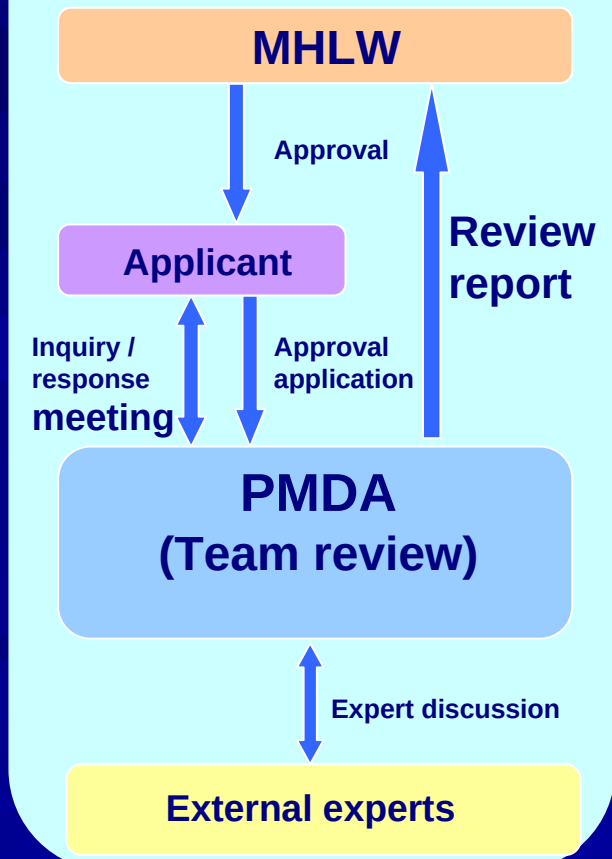
Phase II trials
(Early stage)

Phase II trials
(Final stage)

Phase III trials

New drug application

MHLW／PMDA



PMDA Consultation
(expanded ～２００７)

- ~14 types of Consultation
  - General; Regulatory Framework, Review Process, Application Dossier Format, etc.
  - Development Strategy
  - Quality
  - Safety
  - Clinical Trial; Protocol for each Phase, Critical issues regarding Clinical Data, GCP, etc.
  - Pre-NDA
  - PMS

Responsibilities of MHLW & PMDA

[MHLW]

Planning basic policy, enforcement of administrative measures, such as approval, administrative order, etc. which are based on the law

ex.
- **Final judgment on approval**
- **Directions of withdrawal and issuance of emergency safety information**
- **Safety measures for emergent and significant cases**

[PMDA]

Implementation of work, such as review, examination, data analysis, etc before administrative measures

ex.
- **Review of Pharmaceuticals and Medical Devices GMP/GLP/GCP inspection, Clinical trial etc. consultation**
- **Collection, examination, analysis, assessment and provision of ADR information**

- Japanese regulation of biological products

Scope of the “Biological Products”

- Biotechnology Products
  - cell substrate derived protein products
  - gene therapy products
  - cell / tissue-based products
- Blood Products
- Vaccines
- Antitoxins
- Other Medicinal Products of human or animal origin

Consolidation of Safety Measures for Biological Products

For higher risk products

Information review and corrective actions

Preventing spread of infection

Source materials Manufacturing Post-marketing

"ADD-ON" for Biological Products

Safety measures for source materials incl. donor deferral criteria

- **Establishment requirements**
- **Record retention**
- **Prevention of contamination**

- **Proper labeling/use information provision**
- **Look back/traceablity**
- **Periodic infectious disease surveillance report**

Chemical drug / normal devices

GMP/GQP(Good Manufacturing Practice/Good Quality Practice) : manufacturing /quality control to keep consistent quality of products

Starting materials selection criteria

***e.g.* sterilized condition for aseptic products**

GPSP/GVP: Good Post-Marketing Study Practice/Good Vigillance Prctice *e.g.* safety management of companies to deal with vigilance information

The Requirements for Biological Source Materials

1. General Notices and Requirements
2. Requirements for Human Blood
   i. Source for blood products for transfusion
   ii. Source for plasma-derived products
3. Requirements for human-derived materials
   i. Cell and Tissue-derived materials
   ii. Urine-derived materials
   iii. Other human-derived materials
4. Requirements for animal-derived source materials
   i. Ruminant-derived materials
   ii. Cell and Tissue-derived materials
   iii. Other animal-derived materials

The Minimum Requirements for Vaccines & Blood Products

- MRBP provides critical matters of quality control of vaccines and blood products such as test method and acceptance criteria, control of raw materials, manufacturing process control, storage condition and shelf-life.
- MRBP contents;
  - General notices and requirements
  - Official Monographs
  - Methods of analysis
  - Standard materials
  - Reagents

Major points to consider when registering biological products in Japan

Biological products are reviewed scientifically in PMDA.

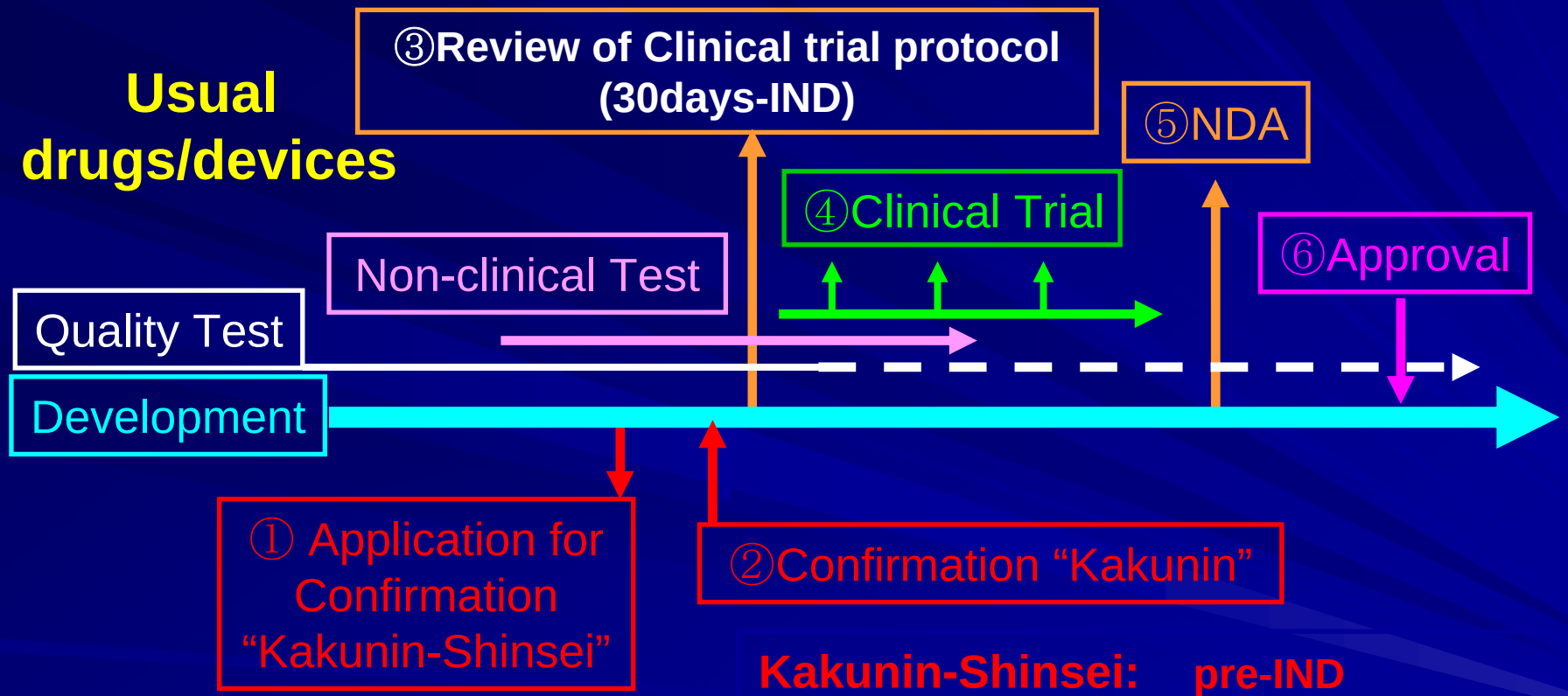
If there are some ICH guidelines, PMDA reviews the application based on these guidelines (ICH-Q5A, Q5B, Q5C, Q5D, Q6B, S6).

In case of making changes to manufacturing processes of products both during development and after approval, PMDA evaluates the changes based on ICH-Q5E.

ICH: International Conference on Harmonization (Japan-USA-EU)

- Japanese regulation of Gene-therapy Products or Cell / Tissue-based Products

Development Process of Gene-therapy Products and Cell / Tissue-based products in Japan under the PAL.



Kakunin-Shinsei: **pre-IND**
Evaluation with respect to the quality and safety of Gene therapy & Cell/Tissue-based products intended for clinical use

ADD-ON for Gene-therapy and Cell/Tissue-based products

Guideline for Gene-therapy Products

Assuring the Quality and Safety of Gene-therapy Products

- Notification No.1062 (15 Nov. 1995)
Rev1. 29 Mar. 2002
Rev2. 28 Dec. 2004

Application for confirmation prior to the first clinical trial : ”Kakunin Shinsei”

Kakunin Shinsei ＝ pre - IND

Guideline for Assuring the Quality and Safety of Gene-therapy Products

This guideline describes the major issues concerning the assurance of quality and safety of the gene-therapy products and outlines the data and information to be addressed by manufacturers when filing an application with respect to the quality and safety of gene-therapy products intended for clinical use.

- **Chapter 1 General provisions**
- **Chapter 2 Manufacturing process**
- **Chapter 3 Specifications and formulation**
- **Chapter 4 Stability**
- **Chapter 5 Preclinical safety studies**
- **Chapter 6 Tests for effectiveness**
- **Chapter 7 Pharmacokinetics and pharmacodynamics**
- **Chapter 8 Manufacturing facilities and equipment**
- **Chapter 9 Ethical consideration**
- **Chapter 10 Miscellaneous provisions**

Recently Confirmed (pre-IND) Gene-therapy Protocols (2003～)

Year	Institution	Target	Vector	Gene	Pts/Cases (Planed)
2003	Anges MG Inc.	ASO	Plasmid	HGF	41 (100) *
2003	Anges MG Inc.	Buerger's disease	Plasmid	HGF	On going (15) *
2007	Takara-bio Inc.	GVHD	Retro	HSV-TK	Planed *
2007	Sanofi-aventis K.K.	ASO	Plasmid	FGF1	More than 10 *

* Reproduced with permission from National Institute of Health Sciences web site http:www.nihs.go.jp/cgtp/cgtp/sec1/gt_prtcl/prtcl-j3.html

As of Dec. 2007

Important Notifications for Cell / Tissue-based Products（1）

- General Principles for the Handling and Use of Cell/Tissue-based Products
  - Notification No.266 (28 Mar. 2001)
- Guidelines on Ensuring Quality and Safety of Autologous Human Cell/Tissue-based Products
  - Notification No.0208004 (8 Feb. 2008)
- Guidelines on Ensuring Quality and Safety of Allogeneic Human Cell/Tissue-based Products
  - Notification No.0912007 (12 Sep. 2008)
- Points to Consider on Manufacturing and Quality Control of Autologous Human Cells/Tissue-based Products
  - Notification No.0327025 (27 Mar. 2008)

Important Notifications for Cell / Tissue-based Products（2）

- Assuring the Quality and Safety of Cell/Tissue-based Products

  ⇒ Application for confirmation prior to the first clinical trial “Kakunin Shinsei”

  – Notification No.906 (30 Jul. 1999)

Kakunin Shinsei = pre-IND

Recently Confirmed (pre-IND) Cell/Tissue-based product Protocols (2001~)

Year	Sponsor	Disease	Cell/Tissue	Auto/Allo
2001	Kirin	Prostate Cancer	Dendritic Cell	Autologous Cell
2001	Kirin	Multiple Myeloma	Dendritic Cell	Autologous Cell
2002	J-TEC	Sever Burns	Epidermis Cell	Autologous Cell *
2004	J-TEC	Osteoarhtritis etc.	Cartilage	Autologous Cell
2006	Terumo	Coronary Infraction	Skeletal Myoblast	Autologous Cell
2007	JCR	GVHD	Mesenchymal Stem Cell	Allogeneic Cell
2007	BCS	Severe Burns	Epidermis and Fibroblast Cell	Autologous Cell

* Approved on 29th Oct. 2007

As of Dec. 2007

- Development of Biological Products used in cancer treatment

Japanese Regulation for Cancer Vaccines and Immunotherapy Products

- Cancer vaccines and immunotherapy products should be regulated as Biological Products.
- In case of Gene-therapy (LMO products) or Cell/Tissue-based Products, there are add-on regulation respectively.
- The efficacy will be reviewed as anti-cancer agents under the guideline for clinical evaluation.

What is “Cancer Vaccines”?

- Antigen/adjuvant vaccines
- Whole cell cancer vaccines
- Dendritic cell (DC) vaccines
- Viral vectors and DNA vaccines
- Idiotype vaccines

- HPV vaccine ???
- HBV vaccine ???

Japanese Regulation for Cancer Vaccines and Immunotherapy Products

- **Peptide/adjuvant vaccines**
- **Whole cell immunotherapy products**

  ex. BCG for intravesical use

  → A monograph of Minimum Requirements for Biological Products was registered newly
- **DC based immunotherapy products**

  Application for Confirmation, as Cell/Tissue-based products, is needed before IND
- **DNA & Viral vaccines**

  are not Gene-therapy products, but・・・

  if recombinant, Application for Confirmation, as Gene-therapy products, is needed before IND

Changes for Anti-cancer Drug Regulation and Clinical Development

- Revised Guideline for Clinical Evaluation on Anti-cancer Dugs (Nov. 2004)
- MHLW established study groups
  - Cancer Combination Therapy (2005)
  - Unapproved Drug (2006)
- PMDA encourages to planning and conducting Multinational Clinical Trials
  - Basic principles on Global Clinical Trials (2007)
- Constructive dialogue with industry, academia and regulatory authority(2007)

Revision of Guideline for Clinical Evaluation

- New guidelines for clinical evaluation of Anti-cancer drugs (issued Nov. 2004)
- Long time passes from the old version (issued on Feb.1991)
- Required the Phase III data before NDA for cancers with large patients population
- Great flexibility for accepting foreign clinical data and clinical development of the oncology drug

Impact of New Revised Guideline

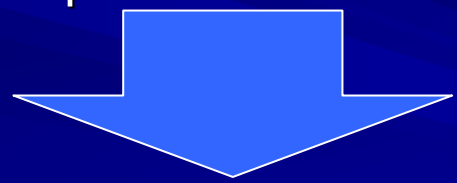
- Increase utilization of foreign clinical data (especially Ph III comparative trial)
  - If a new drug has demonstrated efficacy overseas and if its large safety database is available, then it is advantageous in a smooth and efficient development in Japan
- Increase the importance of development strategy
  - From early stage of clinical development, to conduct of a POC study or a multinational study should be considered for scientific and efficient clinical development.
- Increase dialogs between industry and PMDA

Immunotherapy for Cancer (Cancer Vaccines) Approved in Japan

- **Whole cell immunotherapies**
  - BCG for intravesical use (bladder cancer)
- **Cytokines**
  - interferon
  - （G-CSF）
- **Antibodies**
  - trastuzumab
  - rituximab
  - gemtuzumab ozogamicin
  - iburitumomab tiuxetan
  - bevacizumab
  - cetuximab

Points to Consider on Review of Efficacy of Cancer Vaccines

- Unknown dose-response
- Unique toxicity?
- Endpoint is due to its aim
  - Adjuvant (secondary prophylaxis / prevention)
  - Therapy with / without traditional chemotherapeutic agents / other biologic agents
  - Primary prophylaxis / prevention



Needed multi-arm, parallel design trials; trial design analysis plan
Patient selection and endpoint definition require careful consideration.

Thank you for your attention.

http://www.pmda.go.jp

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