Current status of Japanese Regulation and Development on Biologics

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Pharmaceuticals and Medical Devices Agency (PMDA)

Introduction of PMDA

- NAME: Pharmaceuticals and Medical Devices Agency
- Establishment :

  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 (1st 04’-08’) (2nd 09’-13’)
- PMDA submits performance report to MHLW annually, and that is evaluated by the “IAA Evaluation Committee” for necessary improvement.

3 major work areas of PMDA

Review and Audit for Drugs/ Medical Devices

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

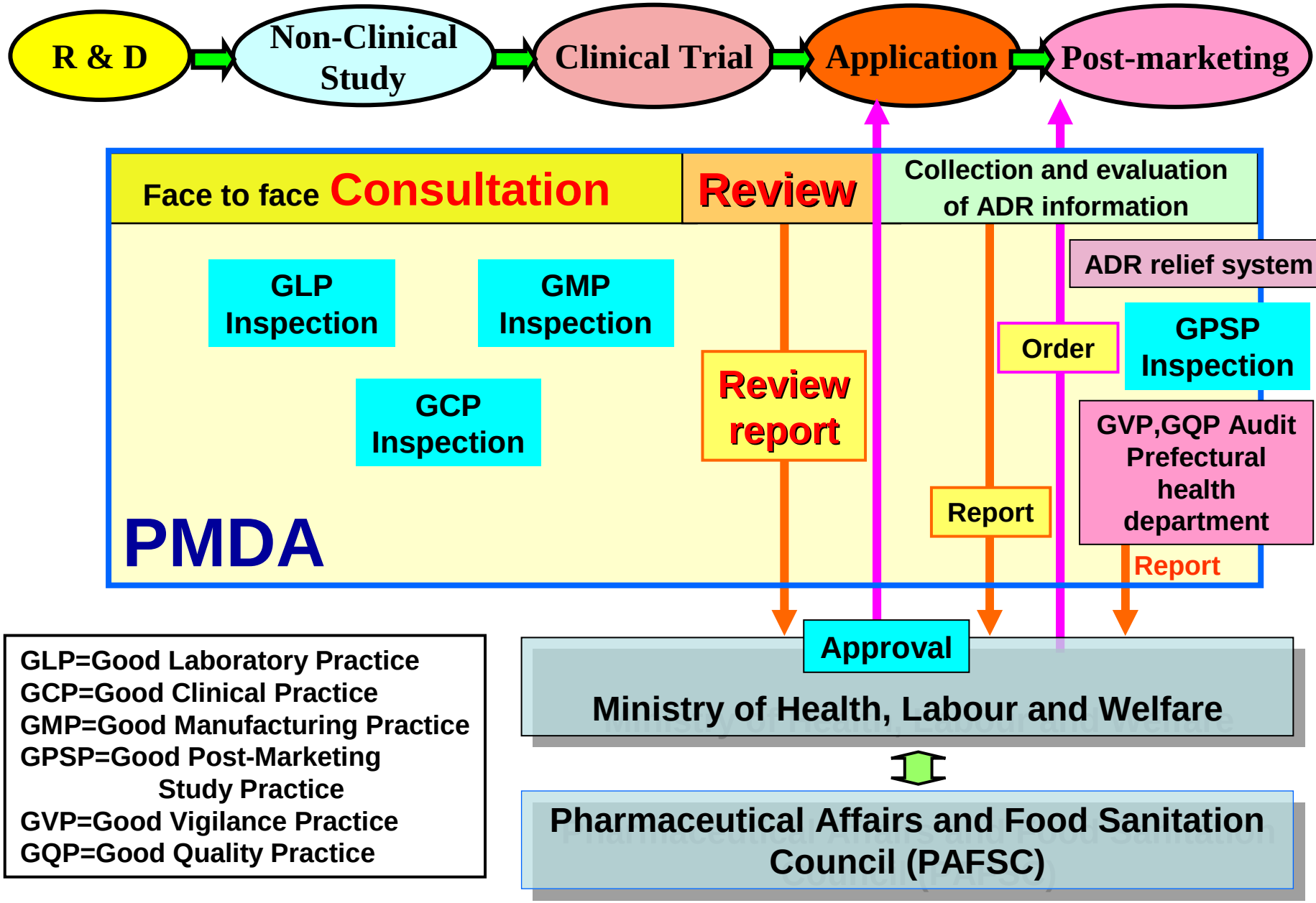
Post-marketing Safety Operations for Drugs/ Medical Devices

- 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

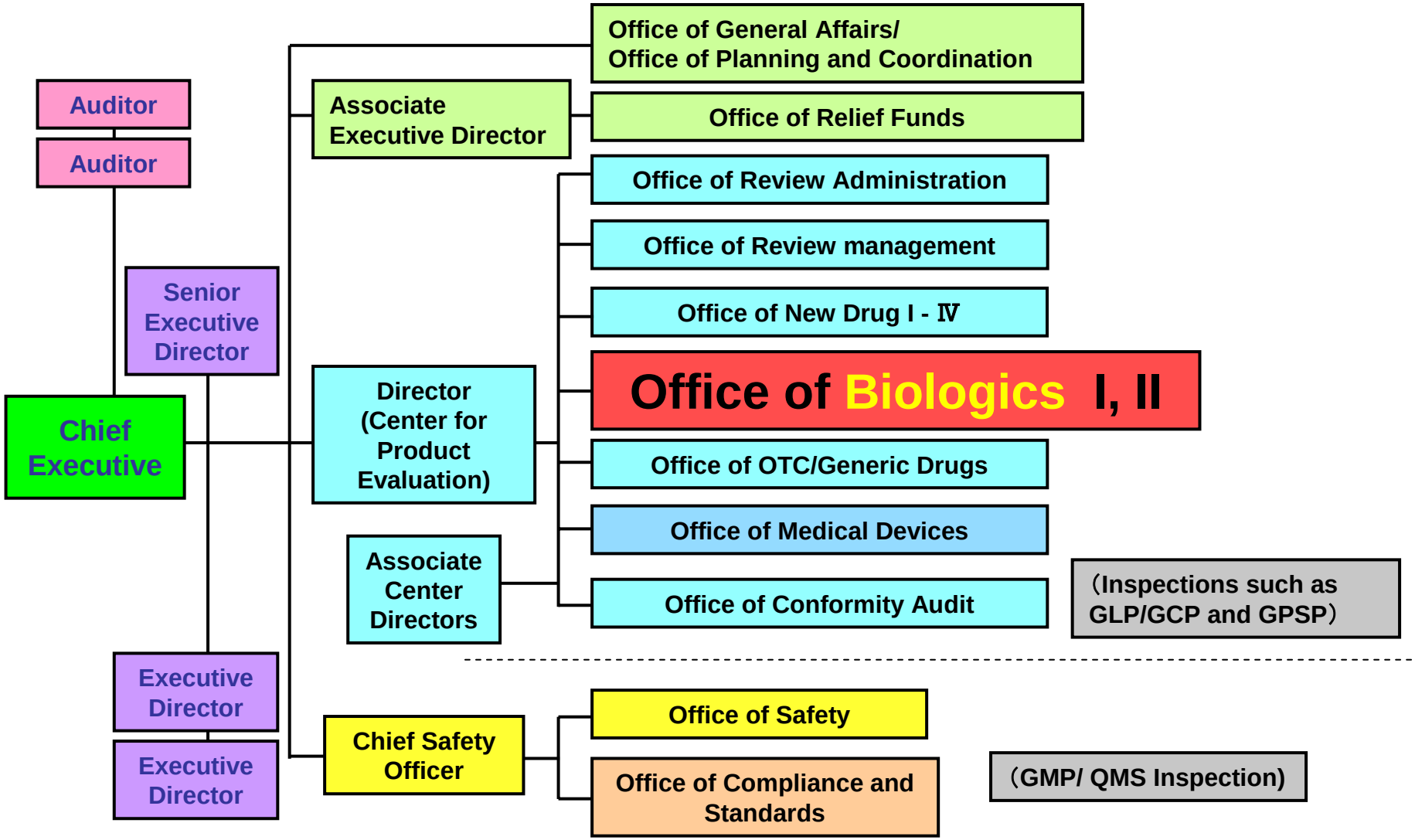
- Provision of Medical Expenses, Disability Pensions etc.
- Relief Service for SMON, HIV-positive and AIDS patients, and HCV-positive and HC patients

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

Organization Chart of PMDA



The work duty of Office of Biologics

1. Office of Biologics I

- Blood Products
- CMC for the Biologics (Pharmaceuticals)
- Advanced therapy products (Gene therapy products)

2. Office of Biologics II

- Biological Products (Vaccines etc.)
- CMC for the Biologics (Medical devices)
- Advanced therapy products (Cell/Tissue based products, Regenerative medicine)

Consolidation of Safety Measures for Biological Products

For higher risk products

Source materials Manufacturing **Post-marketing**

Information review and corrective actions

Preventing spread of infection

"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

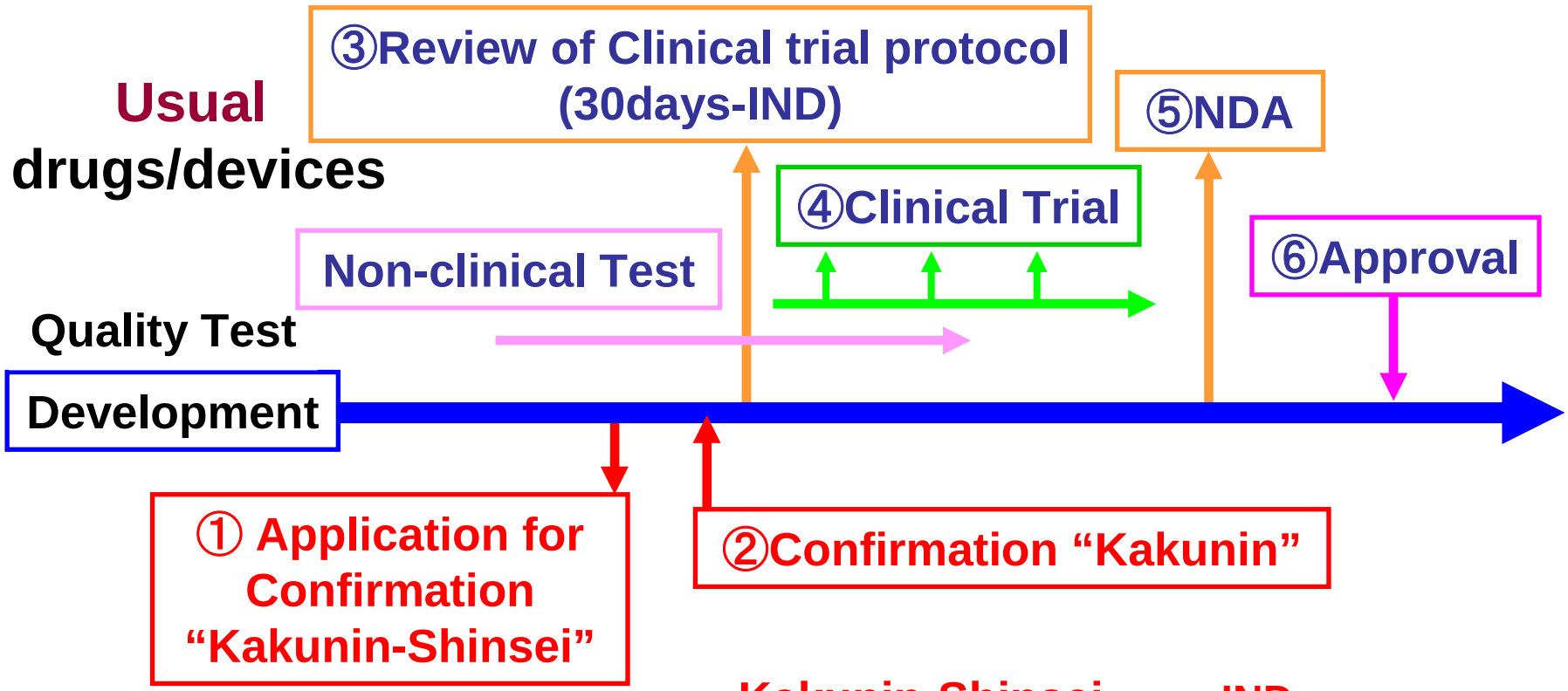
***e.g.* sterilized condition for aseptic products**

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

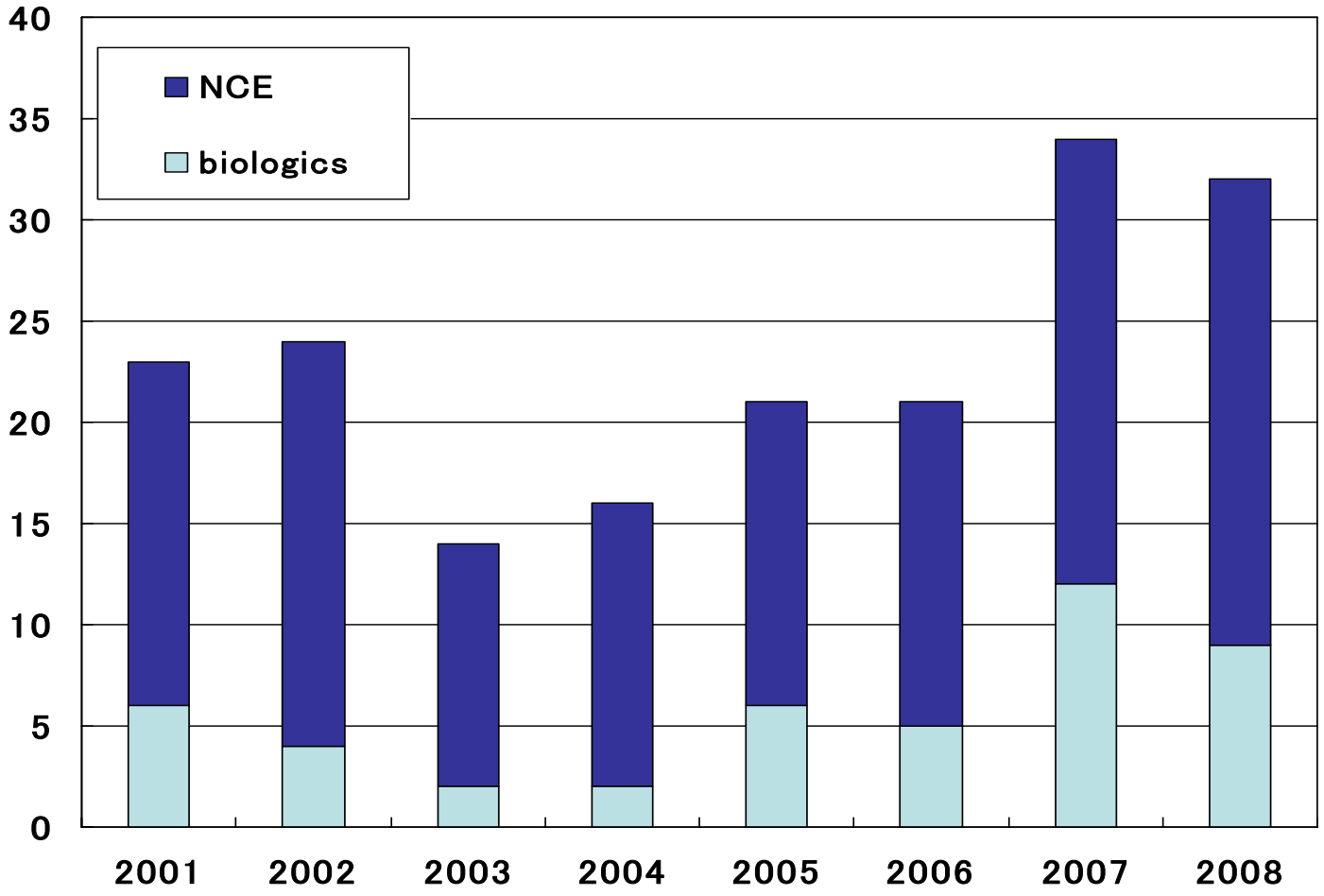
Development Process of Gene-therapy Products and Cell / Tissue-based products in Japan under the PAL.



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

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

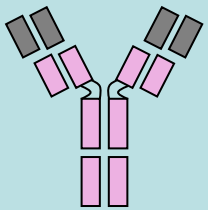
Number of new biologics approved from 2001 to 2008 in Japan



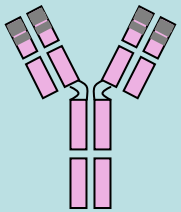
The review reports of these products prepared by the PMDA are publicly available on the Web site.
http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html

New Approved Biologics（1）

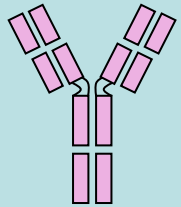
monoclonal antibodies



chimera

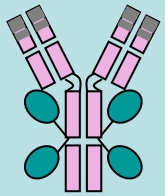


humanized



fully human
(Humira;2008)

Fab
(Lucentis; 2009)



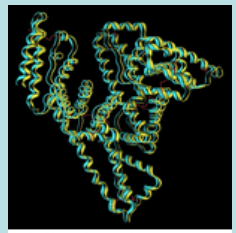
conjugated
(Zebarin; 2008)

human serum albumin (genetical recombination)

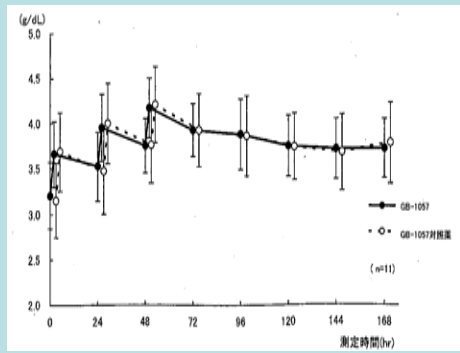
- Medway
  Manufacturer; Mitsubishi Tanabe Pharm

Indications：
Hypoalbuminaemia caused by loss of albumin and reduced albumin synthesis, and hemorrhagic shock

Approved in 2007



X線結晶構造解析
（血漿由来HSA＋rHSA）
Sugio S. et al:
Protein Eng.12(6), 439(1999)
日本蛋白質構造データバンク(PDBj)
より引用

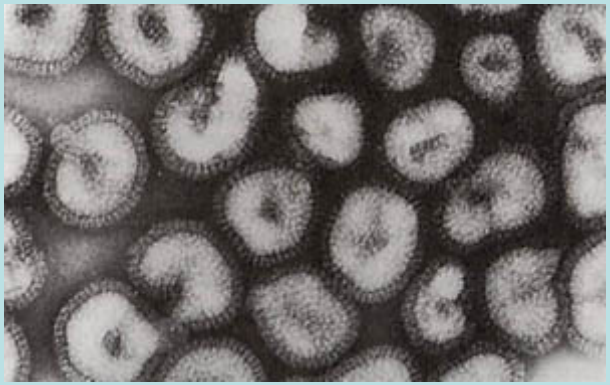


New Approved Biologics（2）

Adsorbed Influenza Vaccines (H5N1)

•Adsorbed Influenza Vaccines(H5N1) “Kitasato”
Manufacturer; The Kitasato Institute
•Adsorbed Influenza Vaccines(H5N1)“BIKEN”
Manufacturer; Research Foundation for Microbial Diseases, Osaka University

Indications; Prophylaxis of influenza (H5N1)
Approved in 2007



Autologous cultured keratinocytes

•JACE
Manufacturer; Japan Tissue Engineering Co., Ltd.

Indications; Serious large burns

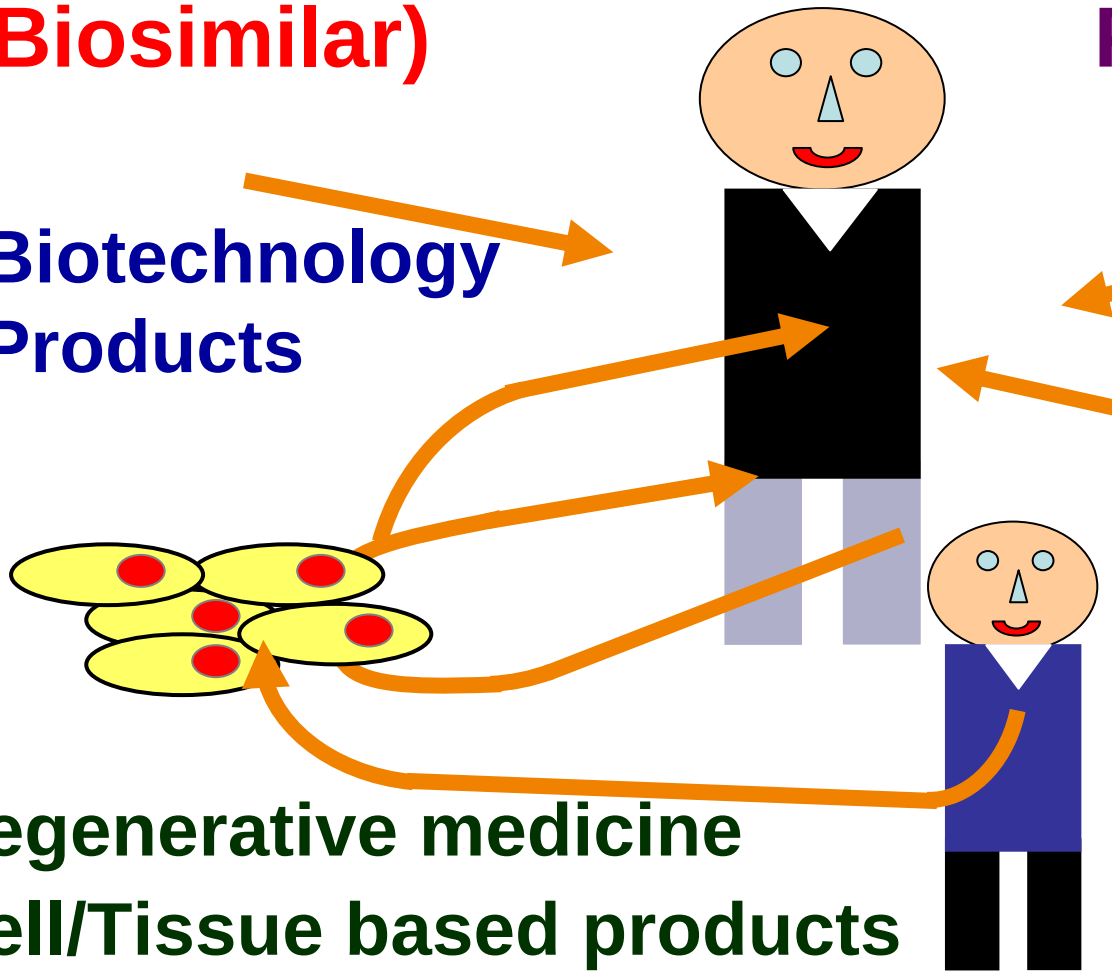
Approvaed in 2007

Near Future Developments

Follow-on Biologics (Biosimilar)

Gene Therapy Products

Biotechnology Products



Vaccines, Therapeutic vaccines, Blood Products

Regenerative medicine Cell/Tissue based products

R&D of the “Biologics” in Japan

- **Biotechnology products**
  - cell substrate derived protein products (antibodies, protein, etc.)
  - animal (plant) factory (GE-animals, GE-plants)
- **Gene therapy products**
- **Cell / tissue-based products** (Regenerative medicine)
  (cells, tissue, stem-cells, ES cells, iPS cells)
- **Vaccines, Antitoxins**
- **Therapeutic vaccines** (immunotherapy products, DNA etc.)
- **Blood Products**
- **Follow-on biologics (Biosimilar)**

Special Districts for Development of Advanced Medical Care (Super Special Districts) 2008 ~

5 Priority Areas	24 Districts

(1) Applications using iPS cells - - - 2

(2) Regenerative medicines - - - 5

(3) Development of innovative medical devices - - - 8

(4) Development of innovative biotechnology-based pharmaceuticals - - - 4

(5) R&D of pharmaceuticals and medical devices crucial to public health - - - 5

For Development of Biologics

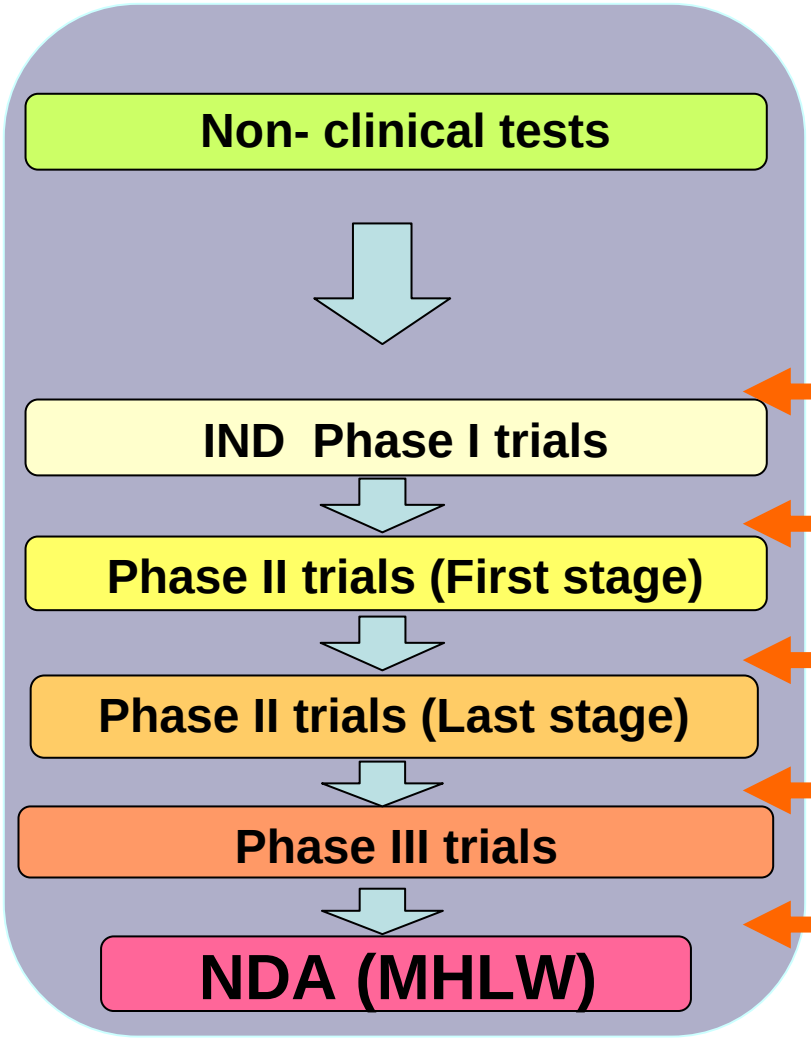
Based on the cooperative interaction between Academia, Industries, Regulatory agency

- **The Consultation from the early stage of the development**
  - **Full-fledged consultation services of the PMDA**
  - **Launching the consultations for PGx/Biomarker (Introduction of the new evaluation approaches)**

- **Establishment of the Guidelines to ensure quality, efficacy, and safety**

Category of Consultation for pharmaceutical development

From non-clinical tests , IND to NDA



Category of Consultation

Administrative Procedures
Quality(bio-)
Safety
PGx / Biomarker
Bioequivalence
Document format on biologics etc.

- Pre-Phase I
- Pre-first period Phase II
- Pre-latter period Phase II
- Post-Phase II
- Pre-NDA

Guidelines for Biologics（1）
-Cell / Tissue-based Products-

- 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 Cells/Tissue-based Products
  - Notification No.0208004 (8 Feb. 2008)
- Guidelines on Ensuring Quality and Safety of Allogeneic Human Cells/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)

Guidelines for Biologics（2）

- **Assuring the Quality and Safety of Gene-therapy Products**
  - **Notification No.1062 (15 Nov. 1995)**
    Rev1. 29 Mar. 2002
    Rev2. 28 Dec. 2004

- **Other related guidelines:**

  ICH Guidelines

  (Quality, Safety, Efficacy, Multidisciplinary)

Guidelines under Development

- **Vaccines**
  - for clinical study
  - for pre-clinical study
  - for adjuvants
- **Regenerative medicine**
  - Cardiac muscle, Cornea etc.
- **Stem cells**
  - iPS cells, ES cells
- **Follow-on biologics (Biosimilar)**

PMDA 3rd International Symposium on Biologics

The Theme of the Symposium

“Follow-on biologics” (Biosimilar)

Thank you for your attention

http://www.pmda.go.jp