

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

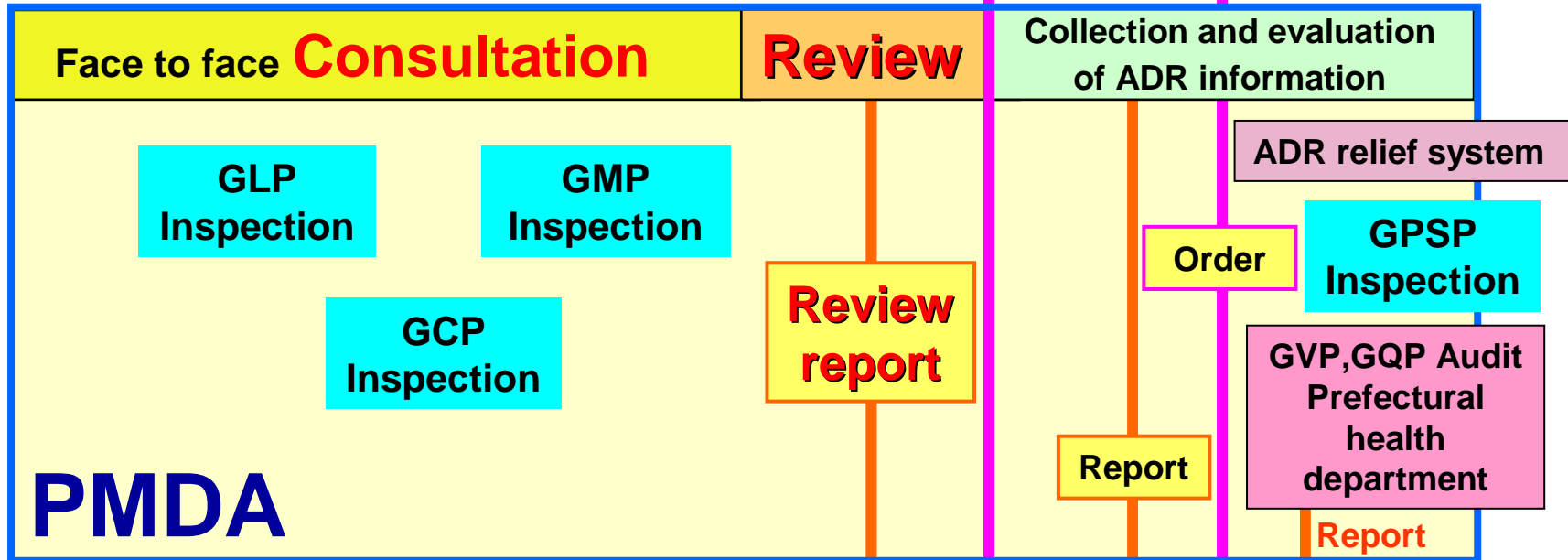
Provision of Information (via the Internet),
Telephone Consultation Services for
Consumers

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



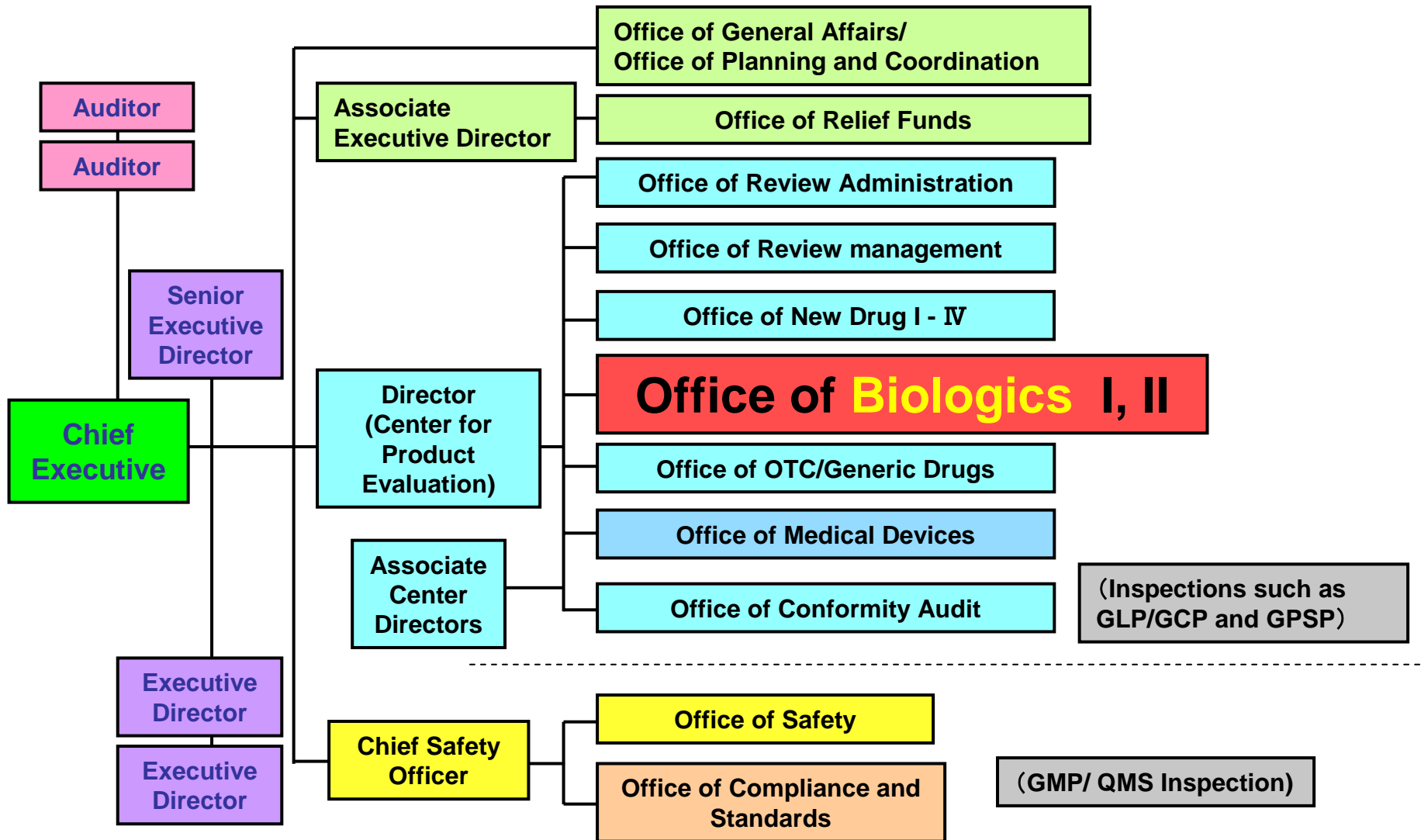
PMDA

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

Approval
 Ministry of Health, Labour and Welfare

Pharmaceutical Affairs and Food Sanitation Council (PAFSC)

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

Information review and corrective actions

Preventing spread of infection

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/traceability
- 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

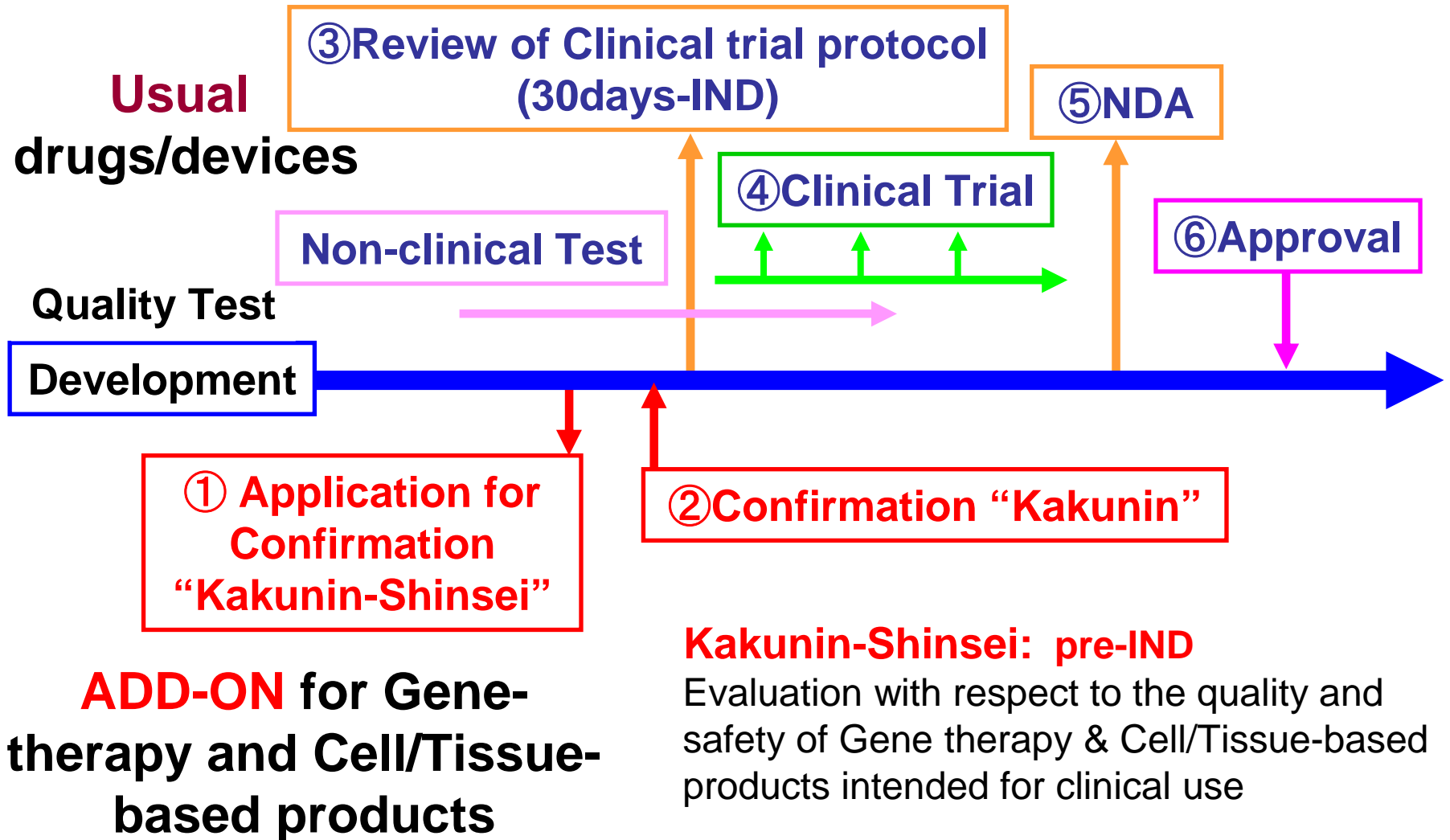
Starting materials selection criteria *e.g. sterilized condition for aseptic products*

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

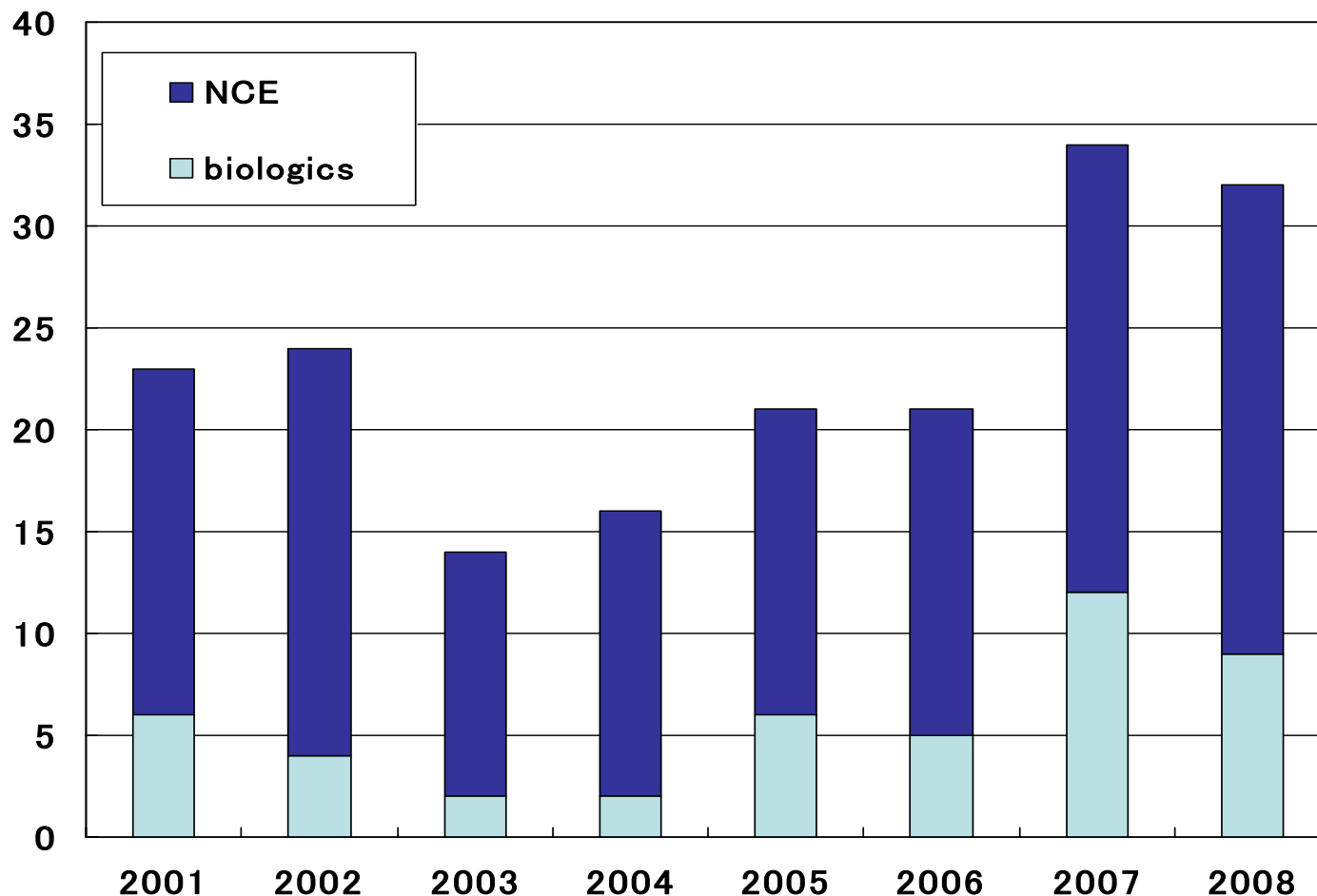
The Requirements for Biological Source Materials

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.



Number of new biologics approved from 2001 to 2008 in Japan



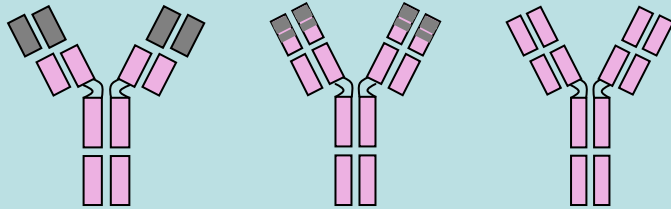
The review reports of these products prepared by the PMDA are publicly available on the Web site.

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)

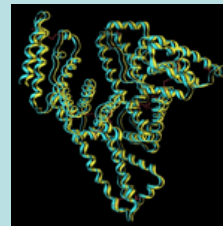
human serum albumin (genetical recombination)

- Medway
Manufacturer; Mitsubishi Tanabe Pharm

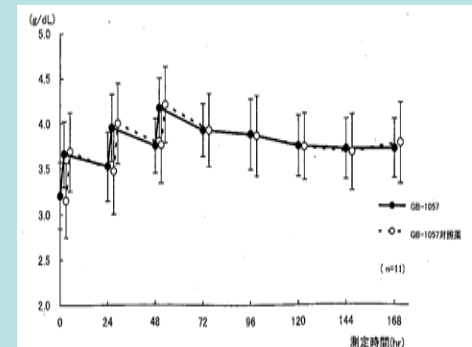
Indications:

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ベース(PDBI)
より引用

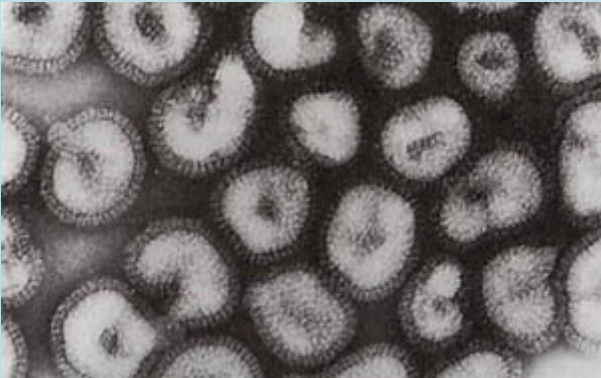


New Approved Biologics (2)

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

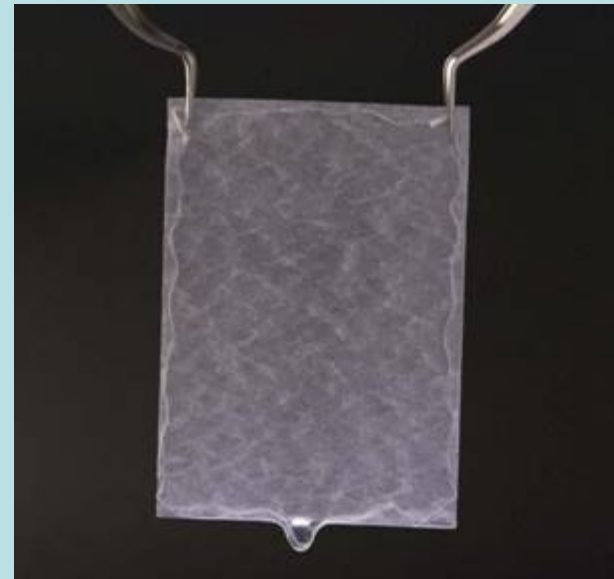


Autologous cultured keratinocytes

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

Indications; Serious large burns

Approved in 2007



Near Future Developments

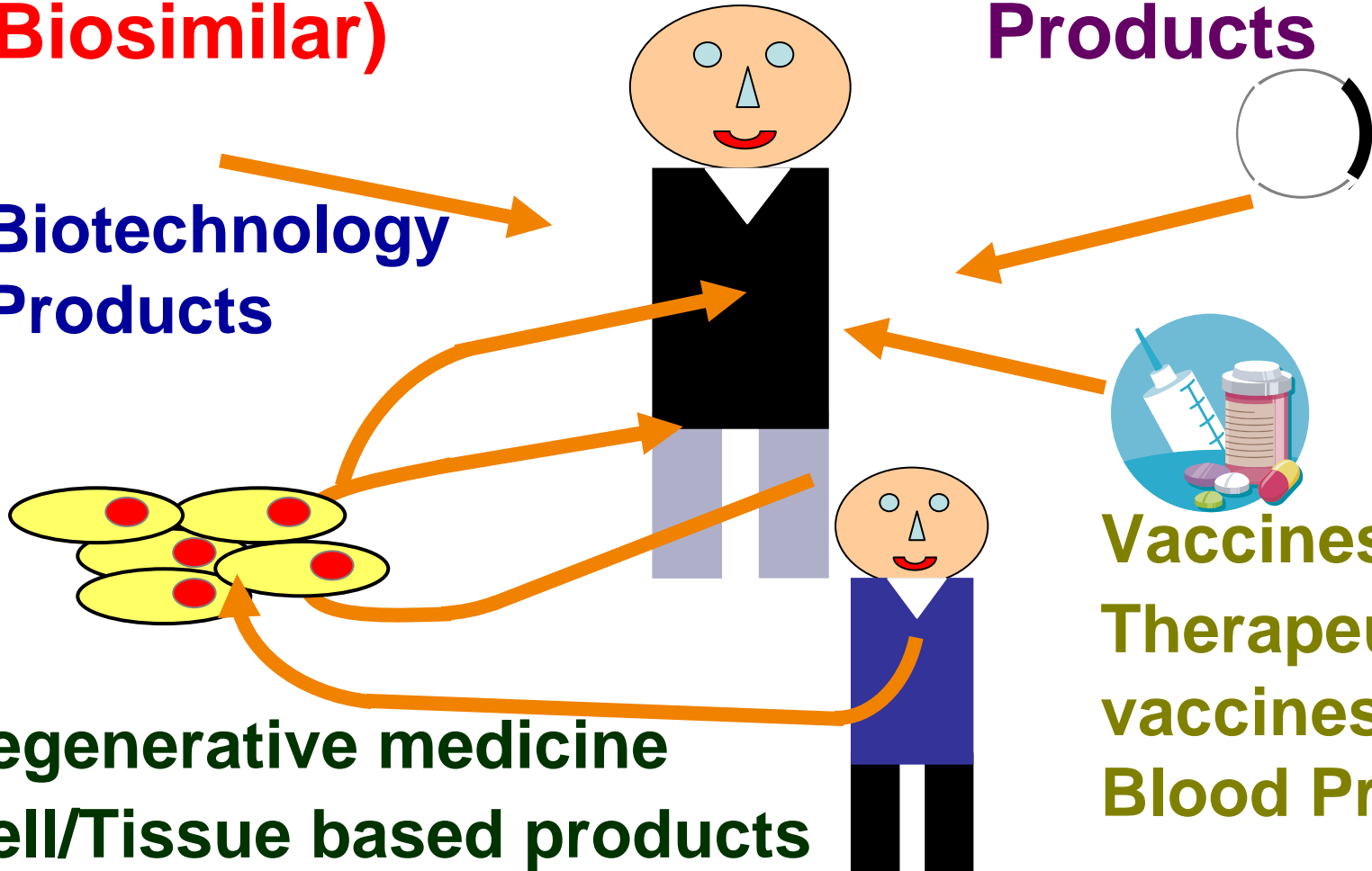
**Follow-on Biologics
(Biosimilar)**

**Gene Therapy
Products**

**Biotechnology
Products**

**Regenerative medicine
Cell/Tissue based products**

**Vaccines,
Therapeutic
vaccines,
Blood 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

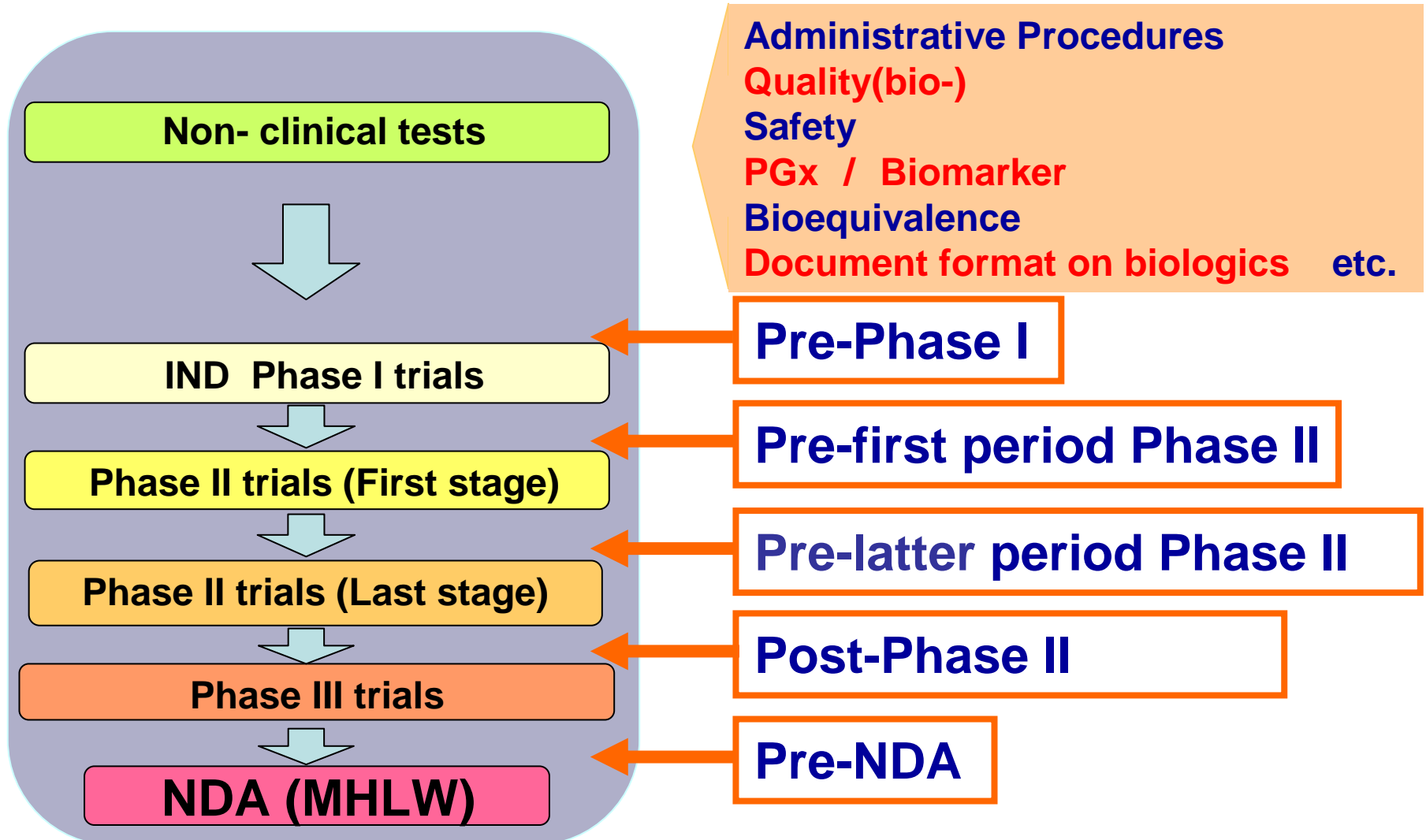
Based on the cooperative interaction between
Academia, Industries, Regulatory agency

- 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



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>