Revision of Pharmaceutical Affaires Law and Establishing Biologics Regulations

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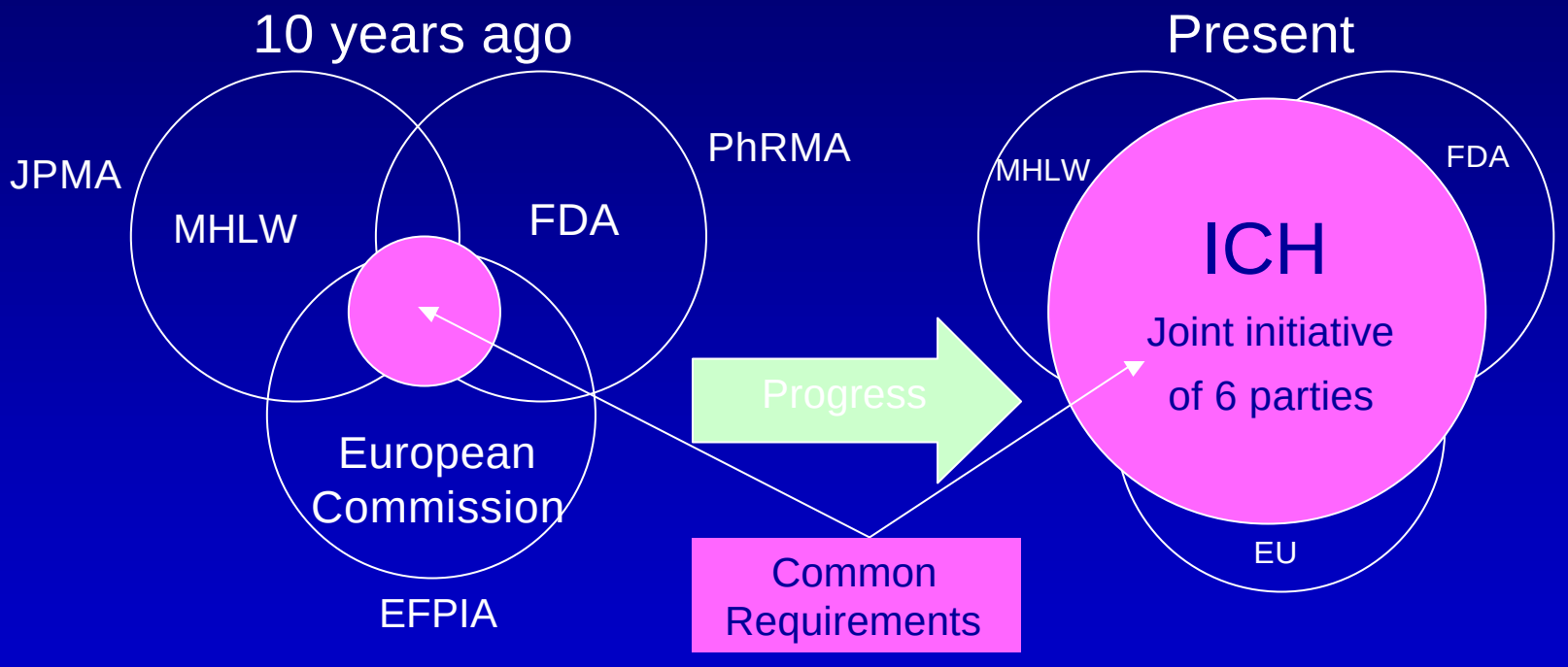
International Conference on Harmonisation

of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

MHLW, FDA, EU/EMEA, JPMA, PhRMA, EFPIA (obs.) WHO, Canada, EFTA

Technical Requirements for NDA（guidelines）



Outcome

More than 50 harmonized guidelines have been achieved in Quality, Safety and Efficacy (including GCP and ICH E5)

Background of PAL Revision

- The scope of the Pharmaceutical Affairs Law (PAL) addresses the necessary regulations for the manufacturing and distribution of products and medical devices to ensure quality, safety and efficacy.
- The law is subject to successive review in response to international harmonization, progress of science and technology, corporate structural variations and other changes of socio-economic circumstances.

  Last revisions：Medical Devices (1994)、Pharmaceutical Products (1996)

  - Age of Life Science (Toward the 21st Century)
    - Progress and application of bio-genomic technology
    - Globarisation of corporate activities and international harmonisation
  - Review of the Pharmaceutical Affairs Law (PAL) toward the needs in the 21st century

Passed Parliamentary Regular Session on 25 July 2002

And Issued on 31 July 2002

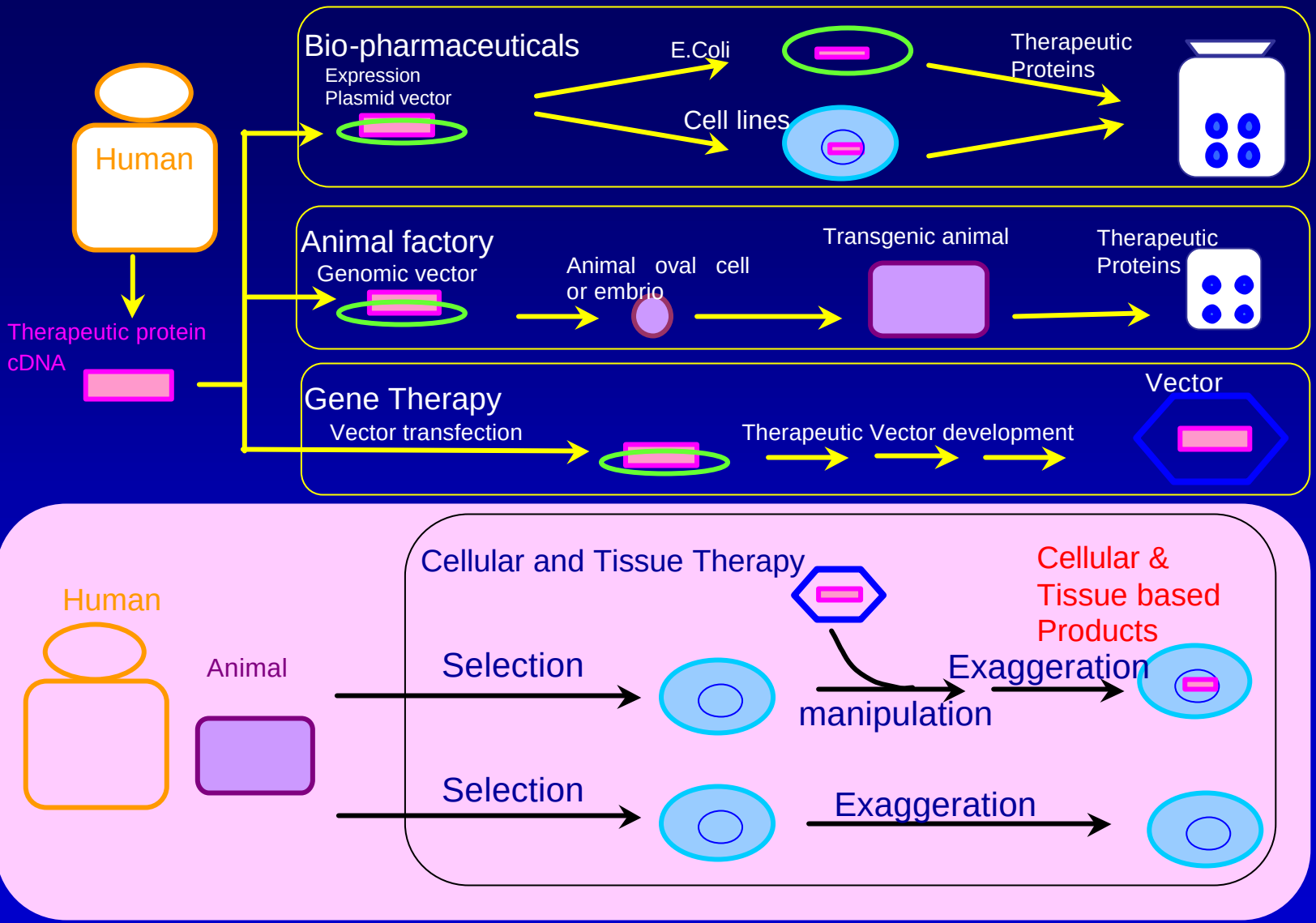
PAL Revision: Three Major Provisions

- Revision of Medical Device Regulation
- Consolidation of Safety Measures for “Bio-Genomic Century”
  → Urgent need to provide comprehensive legal statutes for safety of biological products
- Approval System Revision and Post-marketing Safety Measure Enhancement

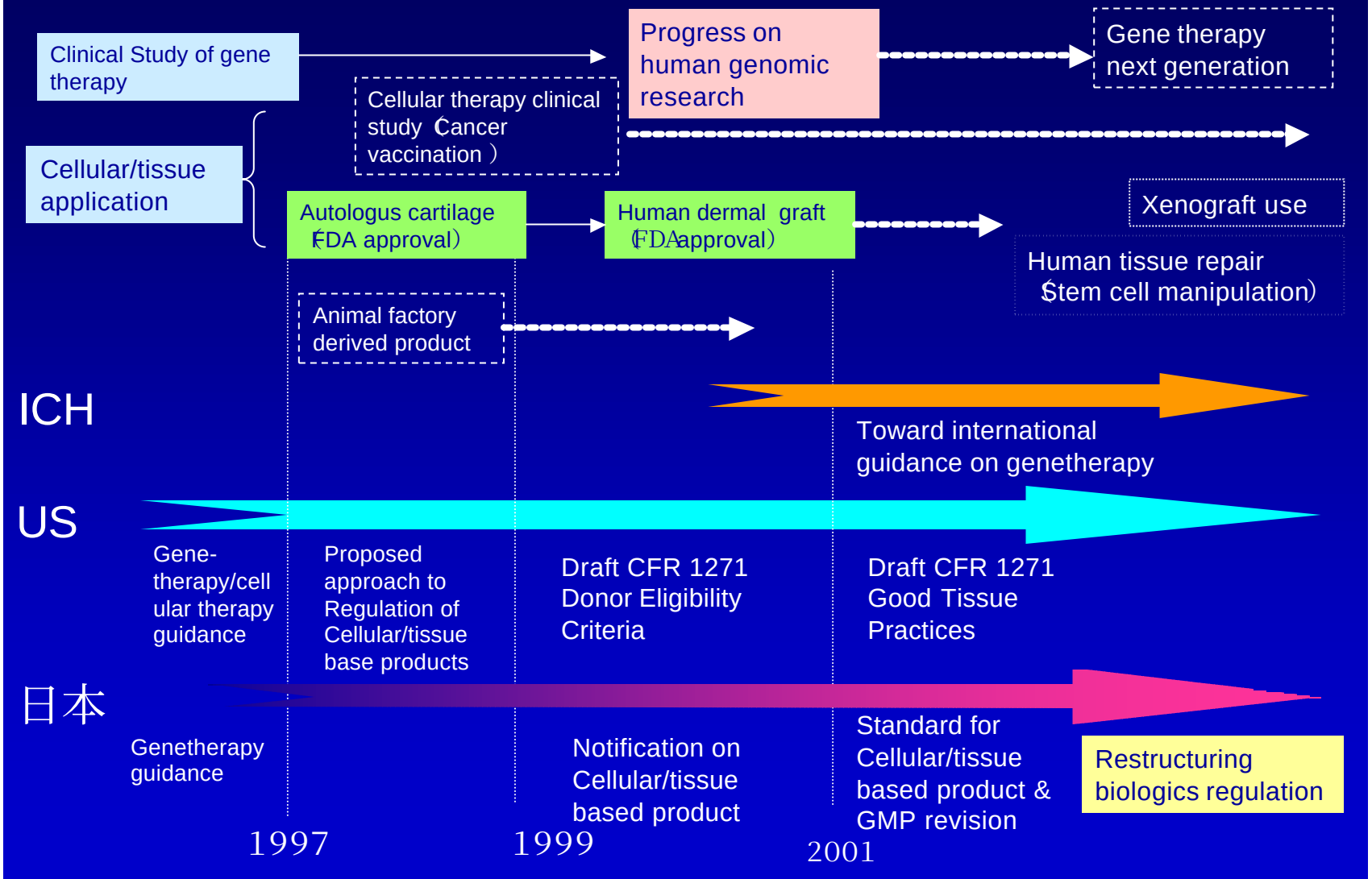
The biological part comes into force in July 2003.

Others in 2005

Biotechnology Derived Products



Trends of Progress of Biotechnology and its Safety Regulation



Biologics from Past to Future

Infectious diseases transmission

- Past:
  - HIV contaminated plasma derivatives
  - Iatogenic CJD through transplantation of Dura mater
- Future:
  - What will happen ?

    while products contribute to regenerative medicines (Human / animal tissue based products/ tissue engineering) are being developed

Comprehensive biologics regulation is requested

- Confront the Risk
- Manage the Risk
- Communicate the Risk

To minimize the risk and hedge the risk

Who is supposed to do what?

Framework of Safety Regulation in Bio-genomic Century

Unified Safety Regulation across the Categories

Overall measures to prevent contamination of infectious agents

Reduction & inactivation of infectious agents

Prevention of emerging / spreading infectious disease , for high risk products (Look back & traceability)

Output of Safety Regulation

- Protection of Patients
- Public confidence on new technology through safety assurance
- Promoting Sound Development

Provision of Promising innovative medicine

Medical Devices	Pharmaceutical Products
Dermal, Cartilage Cell Culture Products	Cancer Immuno-cellular therapy, etc.

Application of Live Human /Animal Tissues

Product development

Promising new indication

Regenerative Medicine (Tissue repair)

Consolidation of Safety Measures for Biological Products (1)

What is “Biological Products” under revised PAL

- Products including ingredients derived from human or biological (excluding plants) source materials (such as cell, tissue, blood, etc.) , which should be subject to particular attention from public health point of view

  e.g. Blood products/plasma derivatives, Vaccines、Recombinant proteins (cell cultured), Cellular/tissue-based products, Gene therapy vectors, etc.

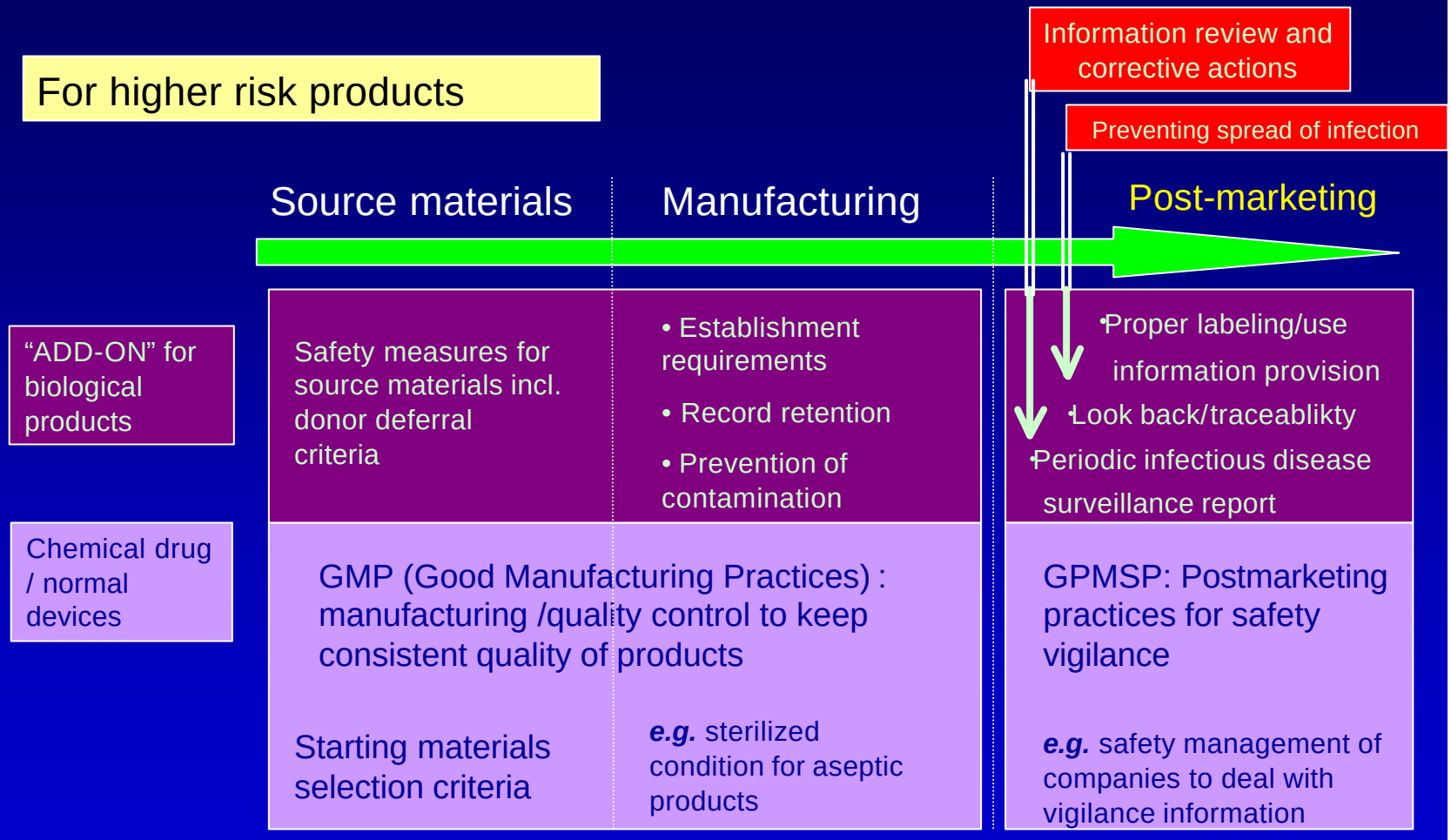
- Major characteristics of biological products

  1. The potential risk of unknown infectious agents derived from the source materials cannot be ruled out.
  2. The safety of individual products are affected by each donor profile where the source materials are collected from many unspecified persons/animals.
  3. The means of inactivation of infectious agents are sometimes limited in order to preserve the integrity and function of the products.

“Biological Preparations” under current Article 42 of PAL

Vaccines, anti-toxines, blood products/plasma derivatives

Consolidation of Safety Measures for Biological Products (2)



Preparation for implementation

Drafting Stage of Regulations

What are the biological Products?

- Revised PAL require Minister of Health, Labour and Welfare to designate individual products, advised by Pharmaceutical and Food Sanitation Council (advisory committee)

- Product classification is done, based on sound scientific assessment of potential risk of infection transmission at the Council

Quality and Safety Assessment for Product Designation to "Biological Products" and "Specified Biological Products"

(Ad Hoc Committee on Biological Products)

Theoretical Relative Risk of Infection pertaining to Final Products

- **Higher theoretical risk of infection : Specified biological product** (blood products/plasma derivatives)
- **Lower theoretical risk of infection : Biological product**
- **Others :** Not designated

= Risk of source materials
- Infectious agent
- contamination

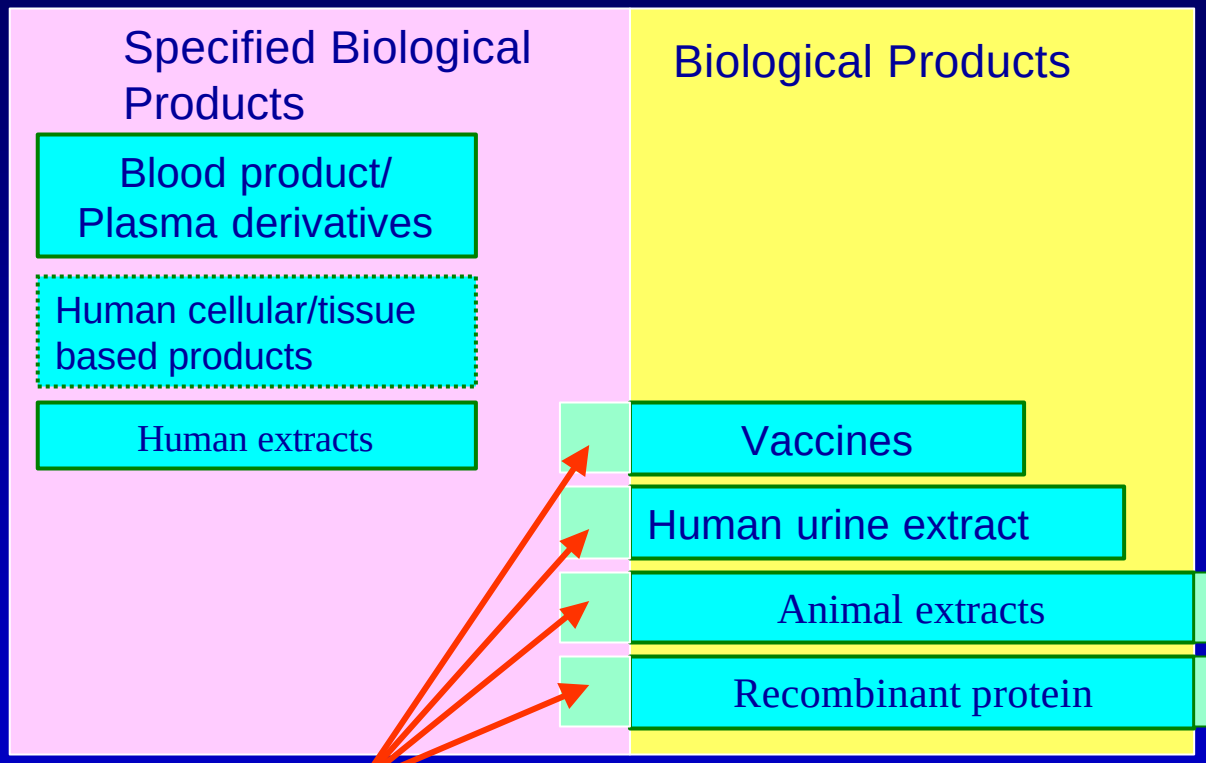
Relative risk of source material
1. Human tissue, blood
2. Pathogenic Virus, Bacteria
3. Cell line (human, mamarian)
4. Animal Extract/component
5. Non-pathogenic bacteria

— Risk reduction measure
- Donor selection
- screening
- inactivation
- elimination

Assured by
Quality control (Standards, Article 42 of PAL)
Quality assurance measure (GMP)

— Safety associated with route of administration, duration, dose
- Safety associated with route
- Safety associated with dose
- Safety associated with length

Designation of Biological Products



- Oral, dermal administration
- Vigorous temperature, chemical treatment
- Use of non-pathogenic bacteria
- Less possibility of human-animal infection

Discussion

Some of those containing Human plasma derivative

Risk is expected equivalent to blood products/plasma derivatives in terms of usage, dose, quantities and duration : **Specified biological products (Recombinant Factor-IV)**

Proposed scope and requirements for Biological products

Safety Measures / classification	Examples of products	Materials	Production control	Postmarketing		
		Source Material Criteria	Record retention	Labeling	Lookback / medical records	Periodic surveillance report
Specified B. P. ※ With particular care for preventing spread of infection	1.Cellular & Tissue Based Drug/Devices (Allogenic)	Donor	+	+	+	+
	2. Human Blood Products incl. plasma	Donor	+	+	+	+
	3. Human tissue / organ / fluid extracts（except urine）	Donor	+	+	+	+
※ Biological Products: Products including ingredients derived from human or biological (excluding plants) source materials (such as cell, tissue, blood, etc.) , which should be subject to particular cares from public health point of view	4. Cellular & Tissue Based Drug/Devices (Autologus)		+	±		+
	5. Animal Cellular & Tissue Based Devices（non-live）	+	+	±		+
	6. Vaccine, antigens, allergenic products		+	±		+
	7. Human urine extracts	+	+	±		+
	8.RecombinantProteins (mamarian cell derived)		+	±		+
	9. Cell Culture Proteins		+	±		+
	10. Animal tissue / organ / fluid extracts (invasive administration)		+	±		+

※ Minister will designate the products under these classes based, according to opinions of P.F.S.Council

+ ：Add-on to chemical drugs。 ± ：flexibility based on the individual characters of the products

“Biological Products”……

Biological Products: Products including ingredients derived from human or biological (excluding plants) source materials (such as cell, tissue, blood, body fluid, etc.) , which should be subject to particular attention from public health point of view. (Article 2.5 of PAL)

For example:

- Vaccine
- Recombinant protein (mammalian cell derived)
- Cell cultured protein, antibodies
- Extract from animal tissue/fluid

Manufacturer:

- Source material selection
- Manufacturing control (revised GMP)
- Record retention for certain period
  - manufacturing batch records
  - sales records to identify consignee
- Periodic surveillance report to MHLW

Labelling :

- Additional labelling requirement to address “Biological products”
- Ingredient information

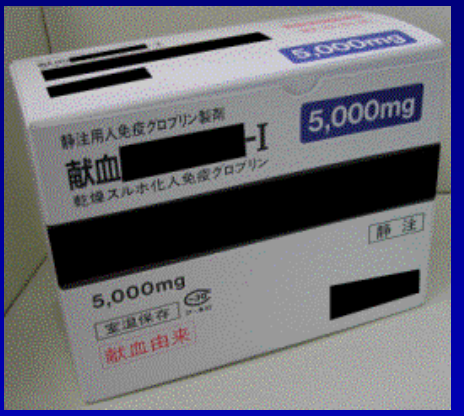
“Specified biological products”….

Specified Biological Product:

Among “biological products” with particular care for preventing onset and transmission of infection (Article 2.6 of PAL)

For example:

- Blood products
- Blood component products
- Plasma derivatives



Additional requirements to biological products:

At medical settings:

- Prior informed consent to patients
- Record retention of patient for certain period

Labelling :

- Information on “risk and benefit”

Who does what?

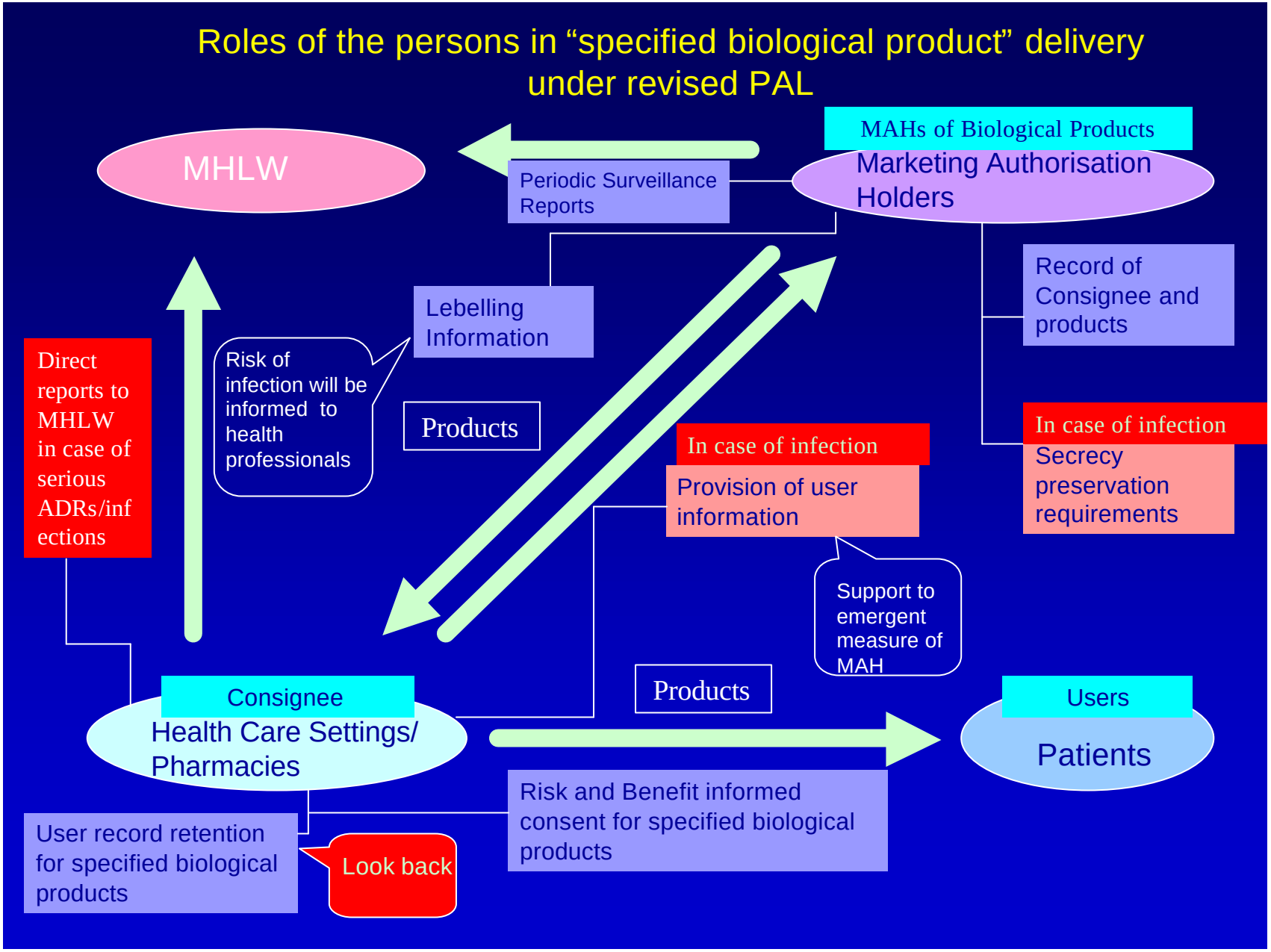
- To minimize public health hazard in case of infection onset in terms of transmission of infections

Revised Pharmaceutical Affairs Law laying down the duties and roles of ….

Manufacturers

Health professionals

Government


Roles of the persons in “specified biological product” delivery under revised PAL
MHLW
MAHs of Biological Products
Marketing Authorisation Holders
Periodic Surveillance Reports
Lebelling Information
Record of Consignee and products
Direct reports to MHLW in case of serious ADRs/infections
Risk of infection will be informed to health professionals
Products
In case of infection
Provision of user information
In case of infection
Secrecy preservation requirements
Support to emergent measure of MAH
Consignee
Health Care Settings/ Pharmacies
Products
Users
Patients
Risk and Benefit informed consent for specified biological products
User record retention for specified biological products
Look back

Example: Cellular/Tissue Based Products (Specified Biological Products)

Regulation / Stage	Pharmaceutical Affairs Law	(Ref.) Public Health Service Act Sec. 351 & Sec. 361 –U.S.
	Manufacturing enterprises outside health care settings	Health care settings & enterprises
Collection of cell/tissue Source Materials	Ethical consideration: Ethics committee, unpaid donation,	------
	Donor eligibility criteria & records (Standards, Article 42 of PAL)	Donor eligibility criteria (21CFR1271-draft)
Facilities & Equipment (incl. Preventing Cross contamination), Quality Management, Record Retention	Revised GMP requirements (including Good Tissue Practice)	cGTP (Good Tissue Practice) (21CFR1271-draft)
Protection of Patients under clinical investigation	IND notification, GCP,	IND review, GCP
Appropriate use	Prior informed consent to patients	
Tracking / traceability in case of infection	Record retention requirements for traceablity (PAL) (both manufacturer & health care professionals)	cGTP (Good Tissue Practice) (21CFR1271-draft)

Retention of Records for Traceability

- How long would it be for?

  (10 years retention of blood product use records at health care settings: 1997 guidance)
- Manufacturing sites（GMP/GTP）
- Distribution chain to manufacturers
- Health professionals

Opinion of Ad hoc Committee on Biological Products

○Specified Biological Products ：

Health Professionals 20 years（patient records）

Manufacturers 30 years（donor records, manufacturing records）

○Biological Products ：

Manufacturers 10 years

（For those containing human plasma derivatives 30 years）

Infection Relief Fund

Although maximum efforts are carried out, impact of onset of newly emerged infection cannot be 100% avoidable……..

Fund for relief to infection associated with biological products

- The Parliamentary request at the time Pharmaceutical Affairs Law passed
- Contributed from manufacturers
- Compensation is paid for the victims of severe infection associated with products (non-civil responsibility)
- The system will be in place in April 2004

Thank you for your attention