Regulatory requirements to prevent viral shedding during gene therapy in Japan

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Shedding of Virus

Viral Product

Patient

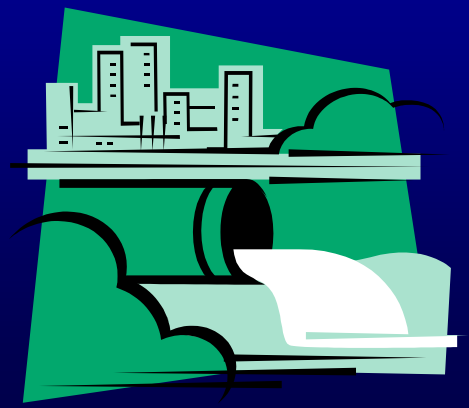
Shedding of Virus into Patients' Blood, Urine, Feces, Sputum...

<In Hospital>

???

???

???



<Out of Hospital>

Current regulatory requirements for viral shedding in Japan

- We have no written document which shows regulatory requirements for viral shedding studies for gene therapy vectors in Japan.

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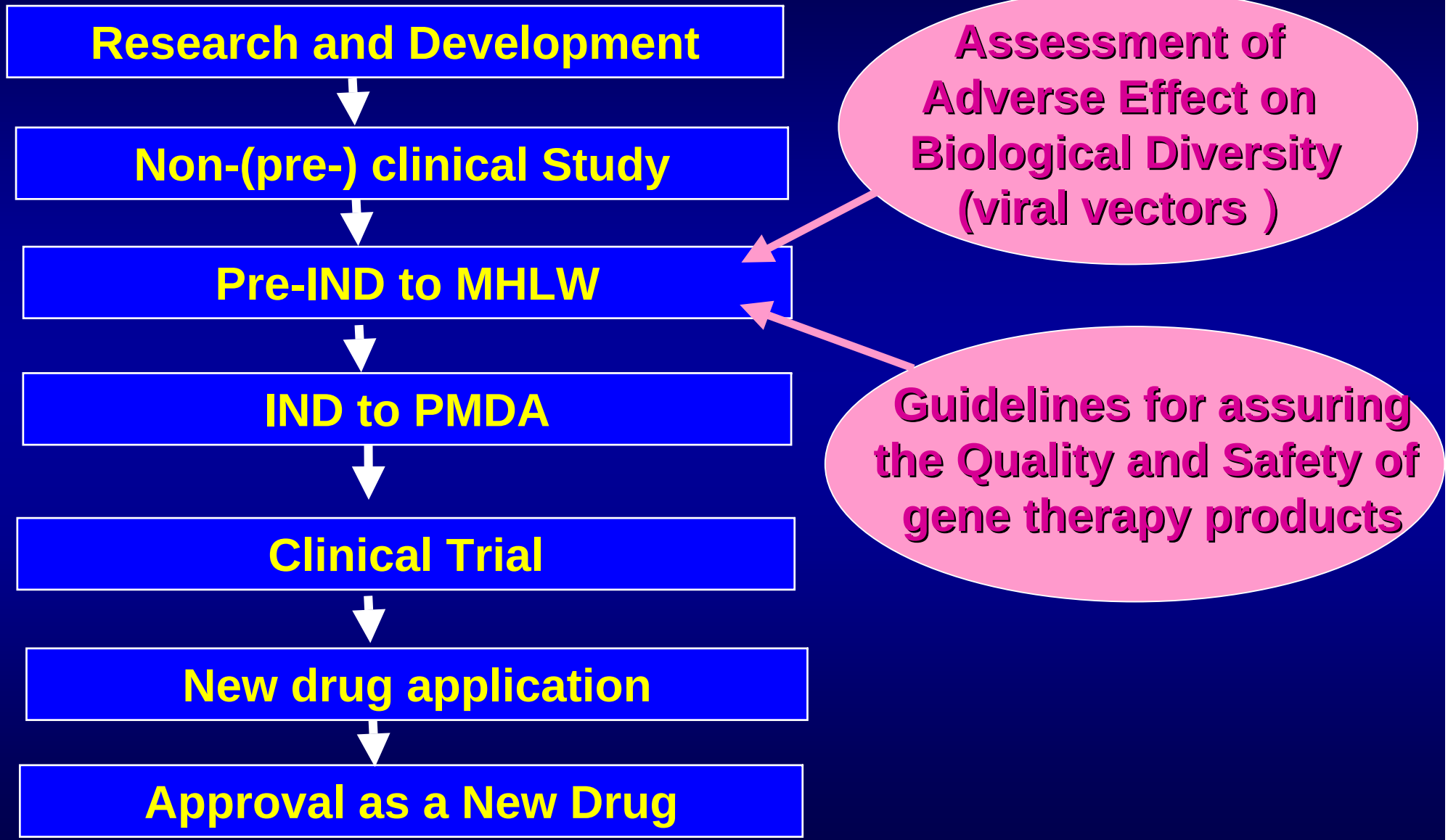
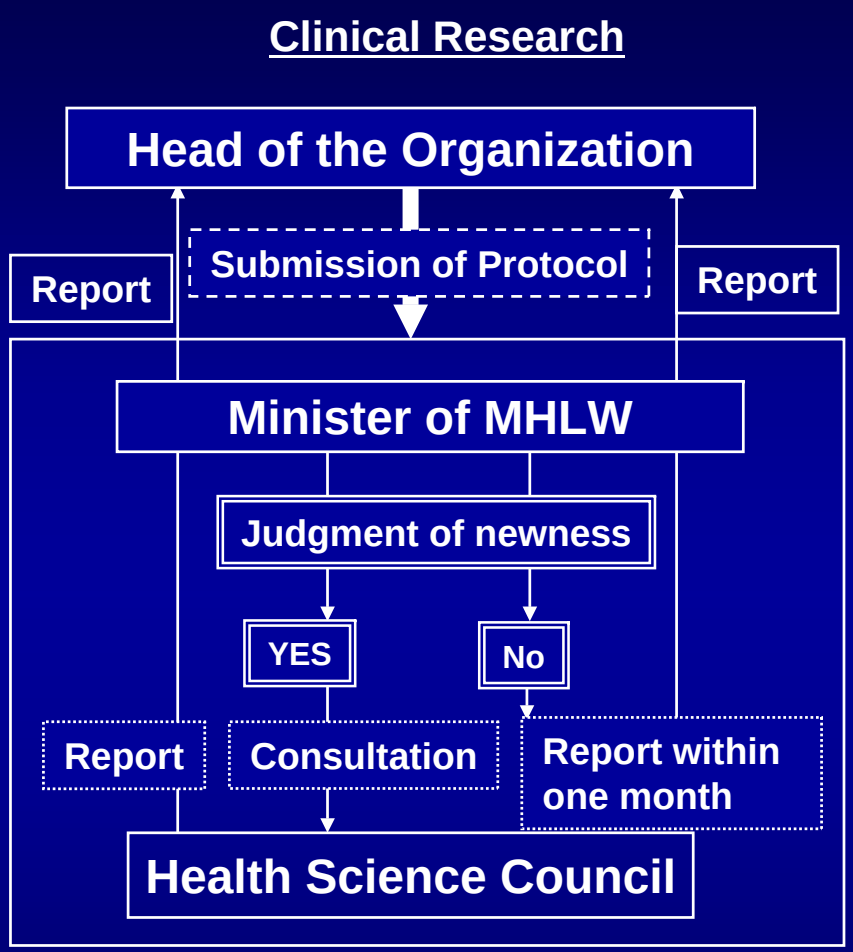
“ Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms ”（ Law No. 97 of 2003 ）

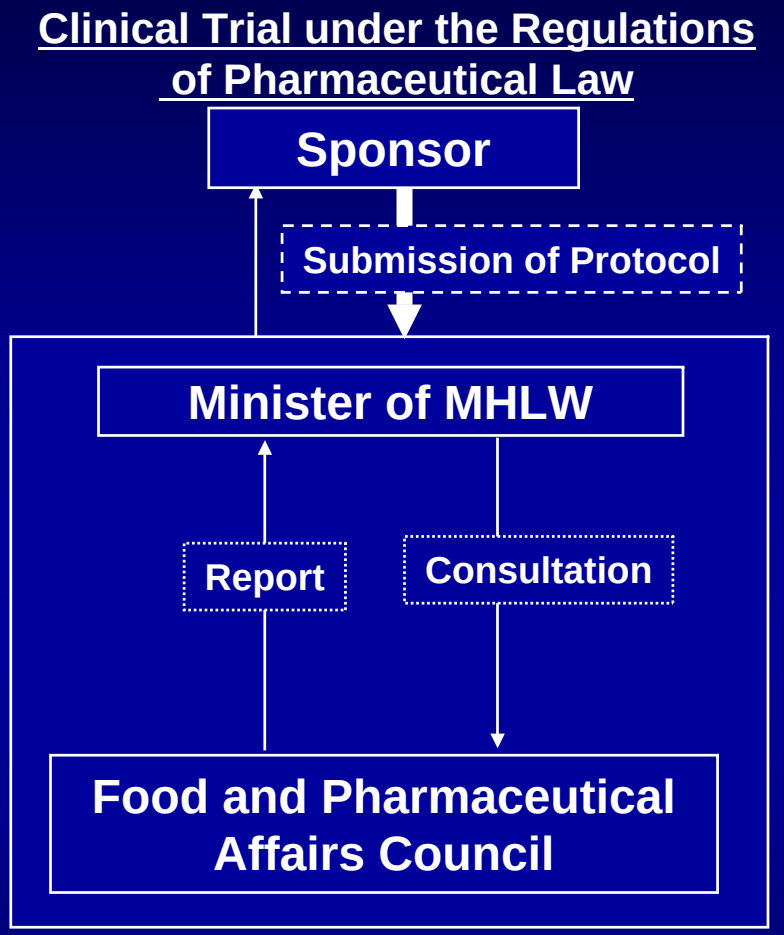
Sponsor is required to prevent the transmission of vectors from patients to 3rd parties in clinical use of gene therapy products, according to the Cartagena Protocol on Biosafety (Type 1Use) .

Regulation of Gene Therapy Products and its Approval



Evaluation of Clinical Study of Gene Therapy in Japan



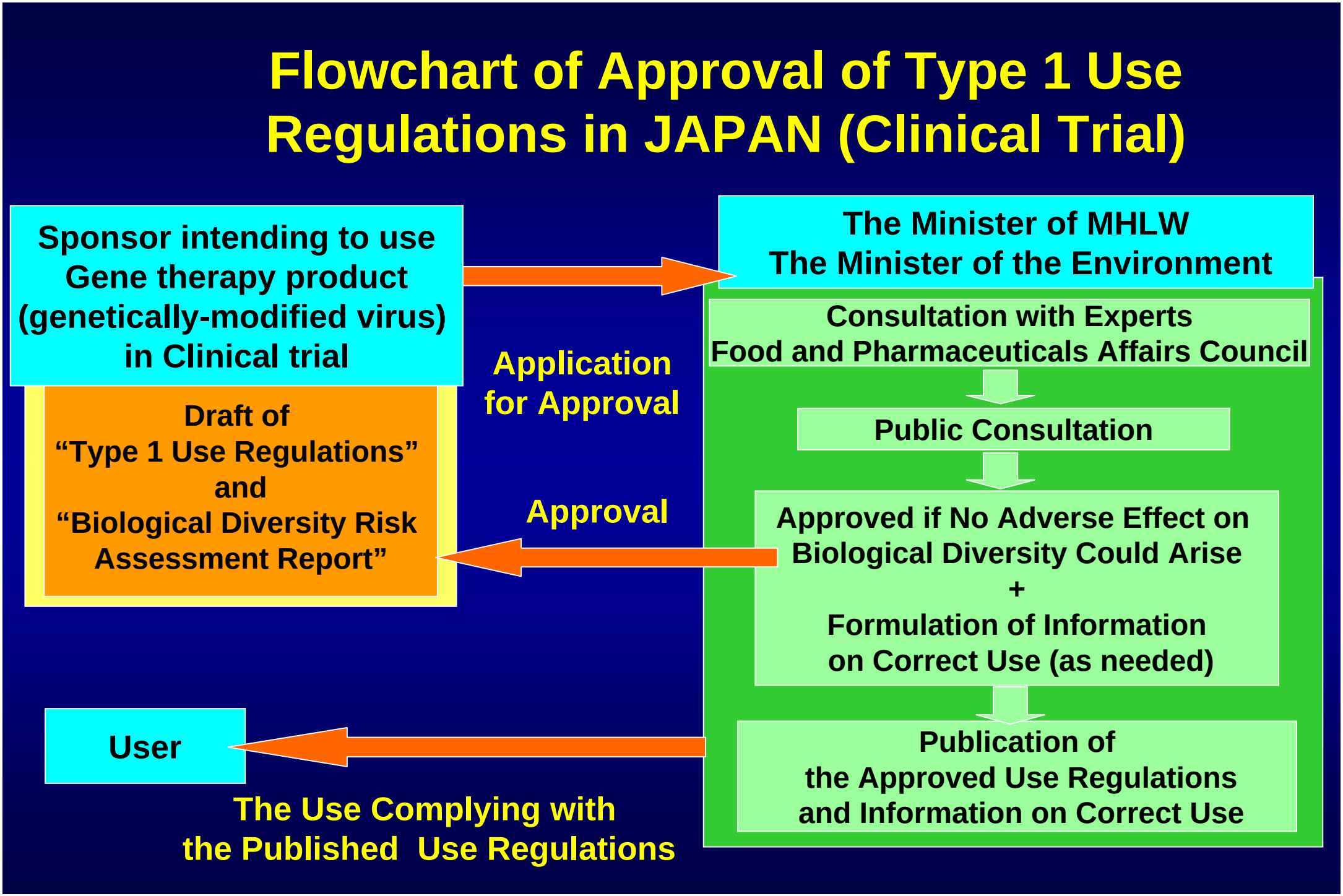


Guidelines for Gene Therapy Clinical Research

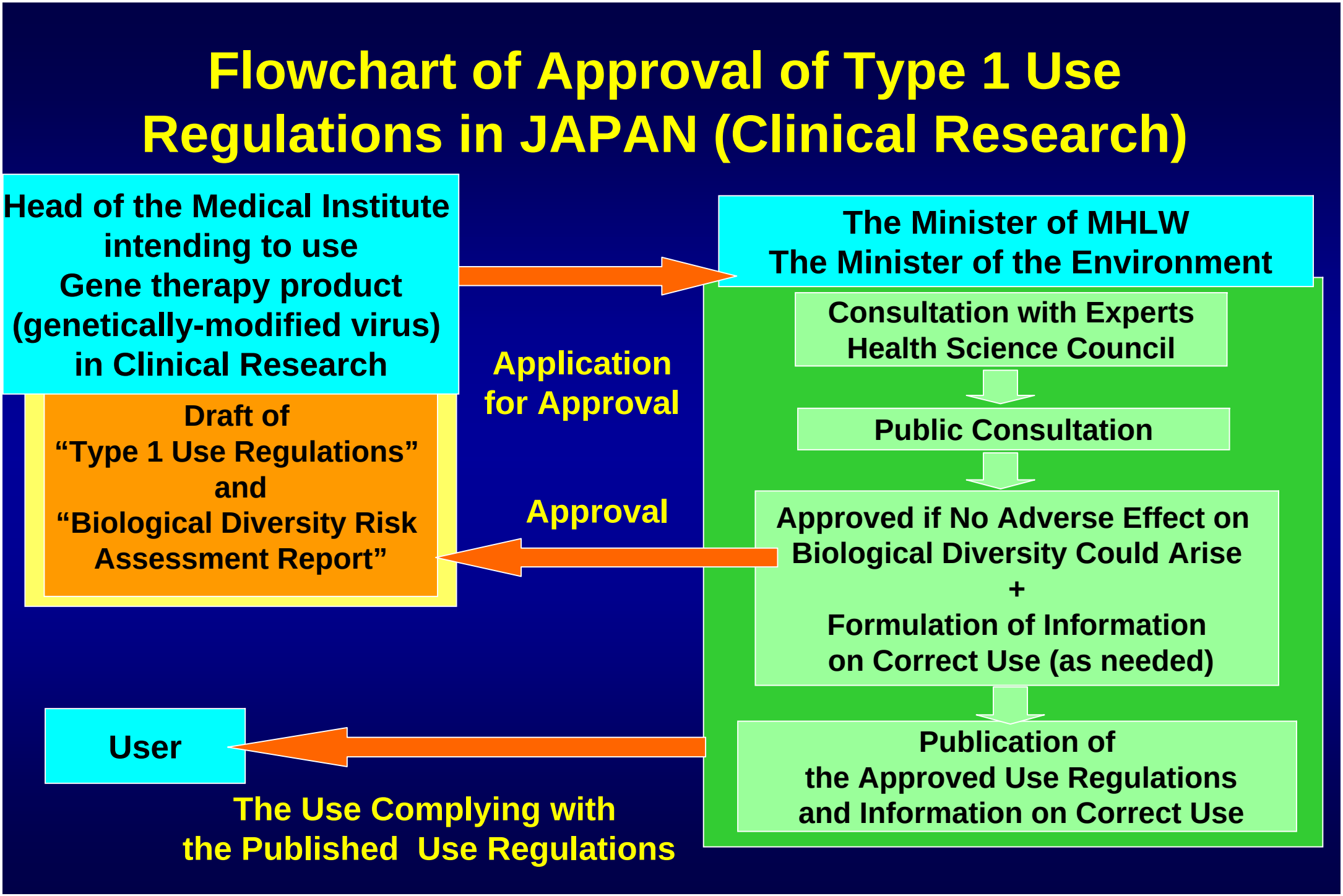
Guidelines for Assuring the Quality and Safety of Gene Therapy Products

Type 1 Use Regulations in Japan

Flowchart of Approval of Type 1 Use Regulations in JAPAN (Clinical Trial)



Flowchart of Approval of Type 1 Use Regulations in JAPAN (Clinical Research)



"Type 1 Use Regulations" and "Biological Diversity Risk Assessment Report"

Information Necessary for Assessment of Adverse Effect on Biological Diversity

I. Information concerning recipient organism or the taxonomical species to which the recipient organism belongs

II. Information concerning preparation of living modified organisms

III. Information concerning the Use of living modified organisms

IV. Assessment of Adverse Effect on Biological Diversity

V. Comprehensive assessment

"Type 1 Use Regulations" and "Biological Diversity Risk Assessment Report"

I. Information concerning a recipient organism or the taxonomical species to which the recipient organism belongs

1. Taxonomical position and State of distribution in natural environment
2. History and present state of Use (including history of use for human or animal drugs, or history and present state of industrial use)
3. Physiological and ecological properties
   - (1) Basic properties
   - (2) Environmental conditions allowing colonization or growth
   - (3) Predacity or parasitism
   - (4) Mode of propagation or reproduction
   - (5) Pathogenicity
   - (6) Productivity of harmful substances
   - (7) Other information (including conditions of inactivation)

"Type 1 Use Regulations" and "Biological Diversity Risk Assessment Report"

II. Information concerning preparation of living modified organisms

1. Information concerning donor nucleic acid
   (1) Composition and origins of component elements
   (2) Functions of component elements
2. Information concerning vector
   (1) Name and origin
   (2) Properties
3. Method of preparing living modified organisms
   (1) Structure of the entire nucleic acid transferred to recipient organism
   (2) Method of transferring nucleic acid transferred to recipient organism
   (3) Processes of rearing living modified organisms

“Type 1 Use Regulations”
and
“Biological Diversity Risk Assessment Report”

II. Information concerning preparation of living modified organisms

4. State of existence of nucleic acid transferred to cells and stability of expression of traits caused by the nucleic acid
5. Methods of detection and identification of living modified organisms and their sensitivity and reliability
6. Difference from the recipient organism or the taxonomical species to which the recipient organism belongs

“Type 1 Use Regulations” and “Biological Diversity Risk Assessment Report”

III. Information concerning the Use of living modified organisms

1. Content of the Use
2. Method of the Use
3. Method of collecting information by person who wishes to obtain approval after the start of Type 1 Use
4. Emergency Measures which should be taken to prevent Adverse Effects on Biological Diversity in case Adverse Effects on Biological Diversity could arise
5. The result of Use in laboratory or Use in an environment similar to that in which Type 1 Use is intended
6. Information obtained from use abroad

“Type 1 Use Regulations” and “Biological Diversity Risk Assessment Report”

IV. Assessment of Adverse Effect on Biological Diversity

1. Property of reducing other microorganisms
   (1) Identification of microorganisms likely to be affected
   (2) Evaluation of concrete details of adverse effect
   (3) Evaluation of likelihood of adverse effect
   (4) Judgment of existence of Adverse Effect on Biological Diversity
2. Pathogenicity
   (1) Identification of wildlife likely to be affected
   (2) Evaluation of concrete details of adverse effect
   (3) Evaluation of likelihood of adverse effect
   (4) Judgment of existence of Adverse Effect on Biological Diversity

“Type 1 Use Regulations” and “Biological Diversity Risk Assessment Report”

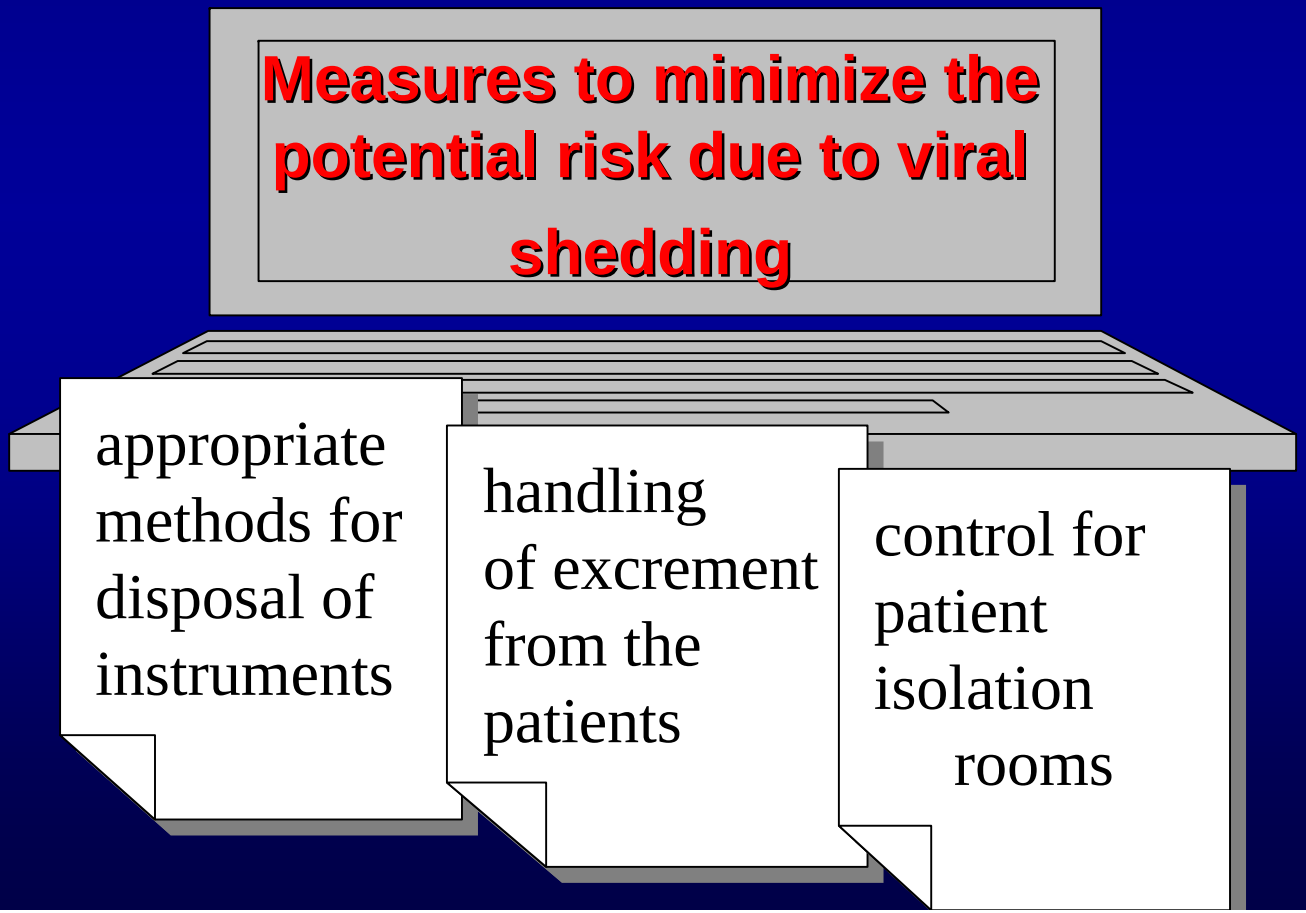
IV. Assessment of Adverse Effect on Biological Diversity

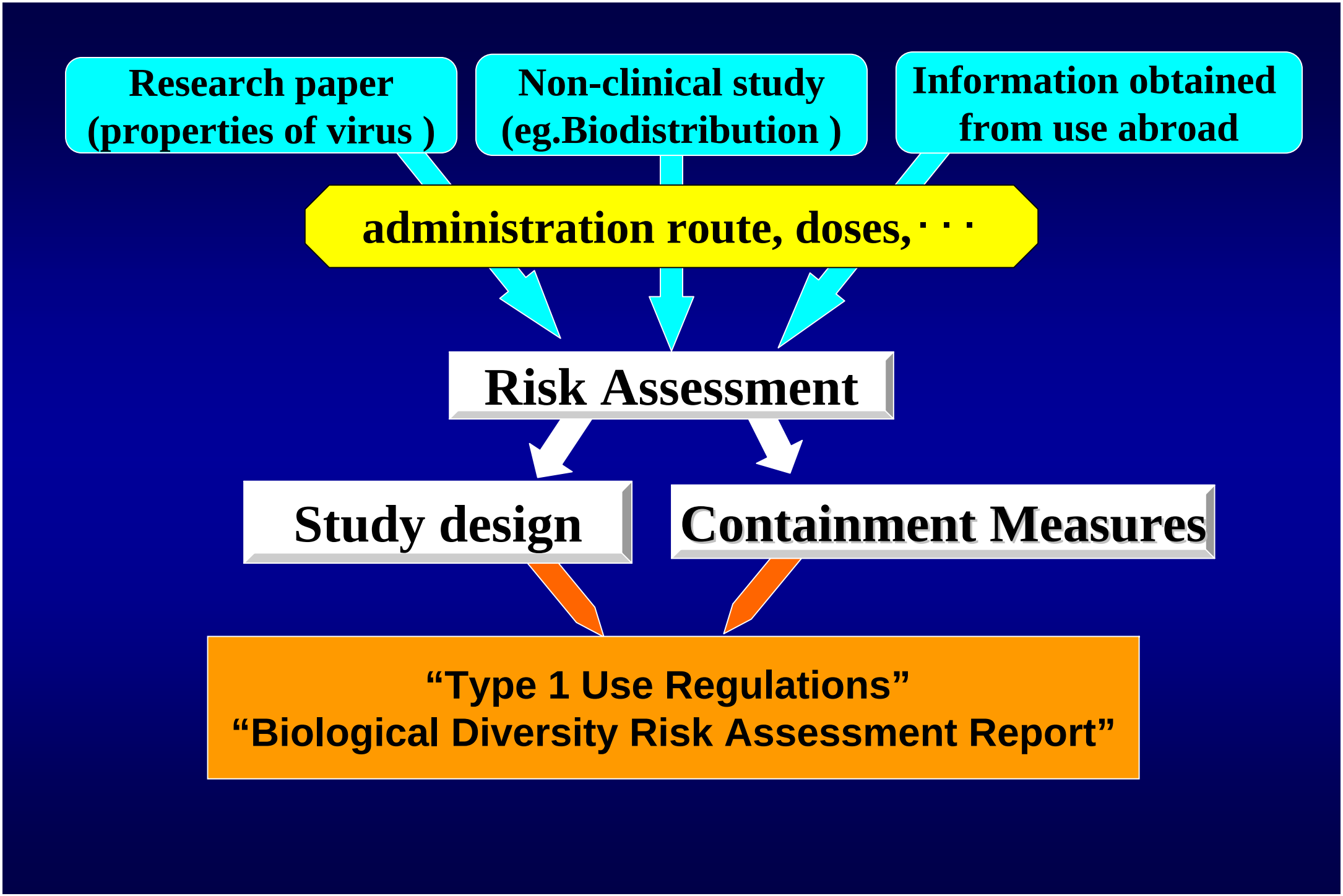
3. Productivity of harmful substances
   (1) Identification of wildlife likely to be affected
   (2) Evaluation of concrete details of adverse effect
   (3) Evaluation of likelihood of adverse effect
   (4) Judgment of existence of Adverse Effect on Biological Diversity
4. Property of transmitting nucleic acid horizontally
   (1) Identification of wildlife or other microorganisms likely to be affected
   (2) Evaluation of concrete details of adverse effect
   (3) Evaluation of likelihood of adverse effect
   (4) Judgment of existence of Adverse Effect on Biological Diversity
5. Other Properties

“Type 1 Use Regulations” and “Biological Diversity Risk Assessment Report”

V. Comprehensive Assessment of Adverse Effect on Biological Diversity

Comprehensive judgment should be performed based on each item listed in section IV.




Research paper (properties of virus)
Non-clinical study (eg.Biodistribution)
Information obtained from use abroad
administration route, doses, · · ·
Risk Assessment
Study design
Containment Measures
“Type 1 Use Regulations”
“Biological Diversity Risk Assessment Report”

Publication of Domestic Law and Regulations

The following website provides information on domestic law, related domestic regulations, list of the approved LMO under the law.

Japan Biosafety Clearing House:

- Domestic Law and Regulations for LMOs
  http://www.bch.biodic.go.jp/english/law.html

- List of Approved LMOs（GT products）:
  http://www.bch.biodic.go.jp/iyaku_kaigi 1.html

Isolation Period after Administration of GT products for Viral Shedding/Cartagena (1)

Vector	Gene	Targeted disease	Medical Institution/ Sponsor	Administration Method	Isolation Period	Cartagena Approval
Retro	adenosine deaminase （ADA）	ADA-deficiency	Hokkaido Univ. Hospital	Bone marrow cells, ex vivo	3 days	2005
	HSV-TK and ΔLNGFR	recurrent leukemia (acute GVHD)	Tsukuba Univ. Hospital /TAKARA BIO Inc.	Lymphocytes, ex vivo	3 days 3 days	2005 2007
	MDR1 （multi-drug resistance 1）	Breast cancer	Cancer Institute Hospital of JFCR	CD34 cells, ex vivo	10 days	2005

Isolation Period after Administration of GT products for Viral Shedding/Cartagena (2)

Vector	Gene	Targeted disease	Medical Institution/ Sponsor	Administration Method	Isolation Period	Cartagena Approval
Adeno	HSV-TK	Prostate cancer	Kobe Univ. Hospital	Bone metastases or Intra-prostatic	3 days	2005
	HSV-TK	Prostate cancer	Okayama Univ.Hospital Kitasato Univ. Hospital	Intra-prostatic	24 hours	2005 2007
Sendai	FGF-2	ASO / Berger's disease	Kyushu Univ. Hospital	Hindlimb skeletal muscles	1 week	2006
AAV	aromatic L-amino acid decarboxylase	Late-stage Parkinson disease	Jichi Medical School Hospital	Intracerebral	72 hours	2006

Action after the Isolation Period is Over (1)

Vector	Gene	Targeted disease	Medical Institution/ Sponsor	Action after the Isolation Period
Retro	ADA	ADA-deficiency	Hokkaido Univ. Hospital	・ RCV (-) in blood ⇒Discharge ・ RCV (+) in blood ⇒Continued isolation ・ RCV (-) →RCV (+) after Discharge ⇒ Re-isolation (until patient tested negative for RCV)
	HSV-TK and ΔLNGFR	recurrent leukemia (acute GVHD)	Tsukuba Univ. Hospital /TAKARA BIO Inc.	
	MDR1	Breast cancer	Cancer Institute Hospital of JFCR	

Action after the Isolation Period is Over (2)

Vector	Gene	Targeted disease	Medical Institution/ Sponsor	Action after the Isolation Period
Adeno	HSV-TK	Prostate cancer	Kobe Univ. Hospital	・ Vector (-) in blood and urine ⇒ Discharge ・ Vector (+) in blood and urine ⇒ Continued isolation ・ Vector (-) →Vector (+) after Discharge ⇒ Re-isolation (until patients tested negative for Vector)
Adeno	HSV-TK	Prostate cancer	Okayama Univ.Hospital Kitasato Univ.Hospital	
Sendai	FGF-2	ASO / Berger's disease	Kyushu Univ. Hospital	
AAV	aromatic L-amino acid decarboxylase	Late-stage Parkinson's disease	Jichi Medical School Hospital	

Containment Measures during gene therapy

- **Blood, body fluid and excrement** from a patient during the isolation period → **Disposal after sterilization**

- **Instruments** used in drug administration (e.g., needle, syringe and tube) → **Disposal after sterilization**

- **Instruments** in contact with blood, body fluid and excrement from a patient

  → **Disposal after sterilization, or sufficient cleaning**

Each medical institute's rules for infectious waste disposal should be followed.

Suitability of monitoring(1)

Patients will be isolated until testing negative for virus, but・・・

- *detection method have not been standardized.*
- *it is difficult to choose the detection method.*

Sensitivity depends on detection methods

Infectivity shows real Existence of virus

Sensitive method=PCR?

Detection sequence

Suitability of monitoring(2)

Patients will be isolated until tested negative for Virus, but・・・

- ***Monitoring should be carried out how frequent?***
  until when?
- ***When virus is detected for long period, such as in case of oncolytic virus therapies, patients must continue to be isolated?***

- **These issues of monitoring of viral shedding should be continuously discussed.**

BACK UP

Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms ”（Law No. 97 of 2003）

“Type 1 Use” means

The Use of living modified organisms without preventive measures against their dispersal into environment.

e.g. Performance of gene therapy in medical Institutes

“Type 2 Use” means

The Use of living modified organisms while taking preventive measures against their dispersal into environment.

e.g. Manufacture of gene therapy vectors in plants