3rd DIA Cell and Gene Therapy Products Symposium in Japan

- Development and Practical Use of Cell and Gene Therapy Products in Japan -

December 13-14, 2018

KFC Hall | Ryogoku, Tokyo

Environmental assessments and shedding studies for gene therapy products in the US and Japan

Kanazawa Institute of Technology

Teruhide Yamaguchi

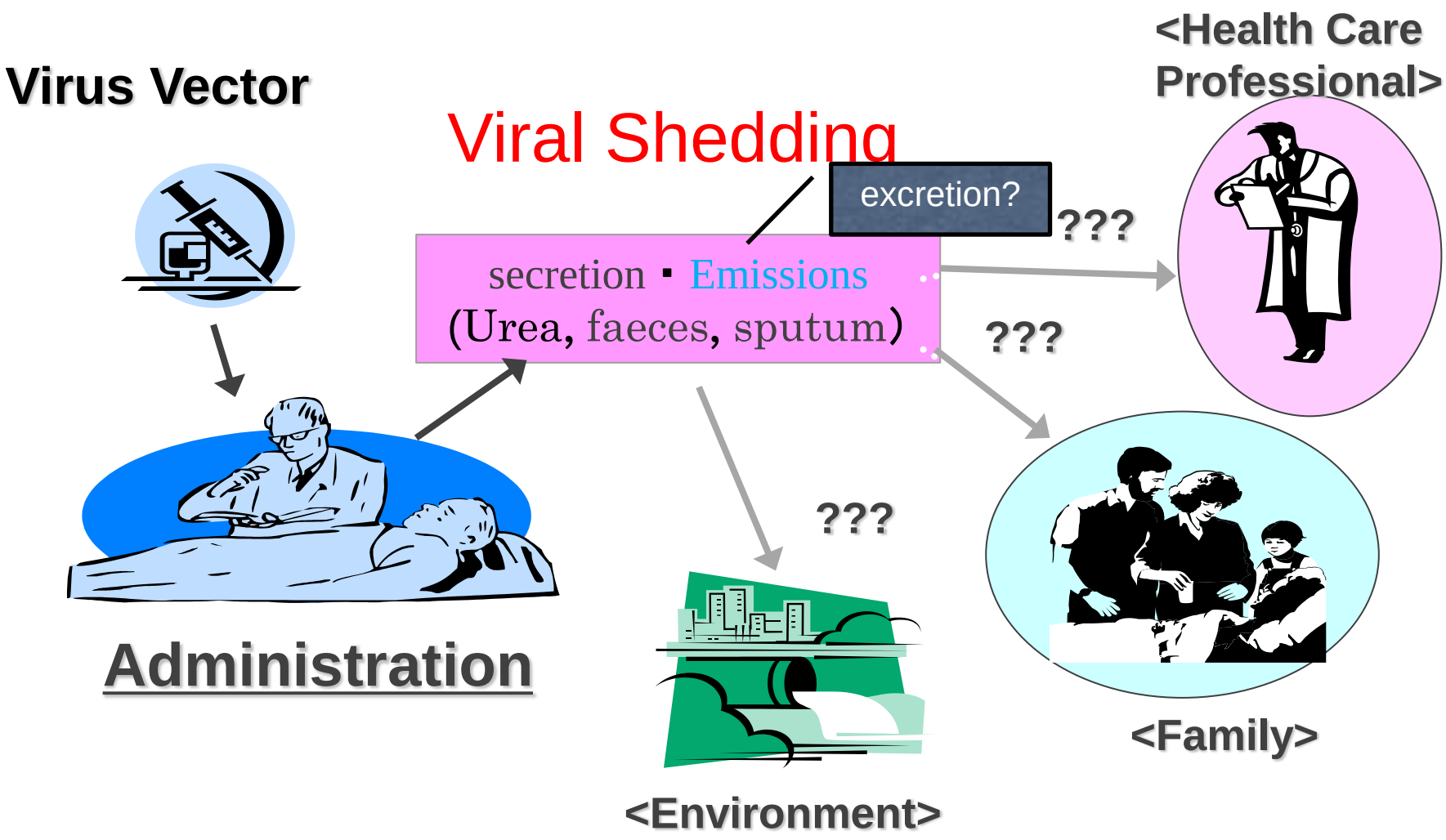
DIA

Disclaimer

- The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to DIA, its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization with which the presenter is employed or affiliated.
- These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. DIA and the DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.

- Environmental assessment of gene therapy products in USA
  Comparison of EA and Biodiversity Assessment

Environmental Assessment for Gene Therapy Products and Virus-shedding Study



Environmental assessment and guideline for viral shedding in USA

- **USA does not ratify the Cartagena Protocol on Biosafety**
- According to US federal law, the sponsor should submit the **environmental assessment about gene therapy product.**
  - **The National Environmental Policy Act of 1969 (NEPA); Revision of Policies and Procedures (Final Rule) 1997**
  - federal law 21CFR25
  - **Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products (GTVV)**
    （Guidance for Industry, FDA CBER, March 2015）
  - **Design and analysis of shedding studies for virus or bacteria-based gene therapy and oncolytic products**
    （Guidance for Industry, FDA CBER, 2015)

FDA Guideline for the Environmental Assessment: IND Approval

- **The sponsor should submit the following data in IND** (21CFR25.15(a))
  - ✓ **Environmental assessment**
  - ✓ **Claim for categorical exclusion**

- **In the case of no categorical exclusion**:
  Extraordinary circumstances indicate that the specific proposed agency action may significantly affect the quality of the environment
  - ✓ Extraordinary circumstances: Specific or unknown risk on human, Risk on Endangered Species of Wild Fauna and Flora (CITES)

- In most cases, IND for a clinical study using a GTVV will not significantly affect the quality of the environment because, in brief, these clinical trials are closely monitored and are limited to a designated study group.

DIA

FDA Review of Environmental Assessment for IND of GMO products

- **Key Issues of Environmental Assessment for Human Gene Therapy Investigational New Drug Applications (INDs).**

✓ Collection of viral shedding data to evaluate the environmental assessment

✓ Measures to mitigate the potential risk for securing the safety of the investigational study

- Environment Reviewer is responsible for evaluation of the environmental risk
- Emergency of replication competent virus is concern risk for replication incompetent virus vector including recombinant viral vaccine
- Recommend to collect the viral shedding data about 10 patients

➡If the viral shedding risk is low, collecting the viral shedding data may be skipped. (Shedding data will be required for EA for marketing authorisation application)

- If the data or monitoring protocol is not enough, FDA submit the clinical hold to the sponsor (especial to replication competent virus vector)

FDA Environmental Assessment of Human Drug and Biologics Applications（BLA)

- **BLA of gene therapy products：the sponsor should submit EA**

➢ categorical exclusion（Substances that Occur Naturally in the Environment）are;

- ✓ contain functional protein-coding sequences from one or more species within a *single* genus to “occur naturally in the environment” for purposes of 21 CFR 25.31(c).
- ✓ differ from a wild-type substance only in attenuating point mutations or deletions to be substances that “occur naturally in the environment” for purposes of 21 CFR 25.31(c)
- ✓ have been killed or inactivated by undergoing a specific manufacturing step designed to eliminate their ability to replicate to be substances that “occur naturally in the environment”
- ✓ consist of genetically-modified human

FDA Environmental Assessment of Human Drug and Biologics Applications：（BLA)

- **BLA of gene therapy products：the sponsor should submit EA**
- **Identification of Substances Subject to the Proposed Action**

“Identification of Substances Subject to Proposed Action”; “Identifying and Assessing Potential Environmental Effects”; “Mitigation Measures”; and “Alternatives to the Proposed Action.”

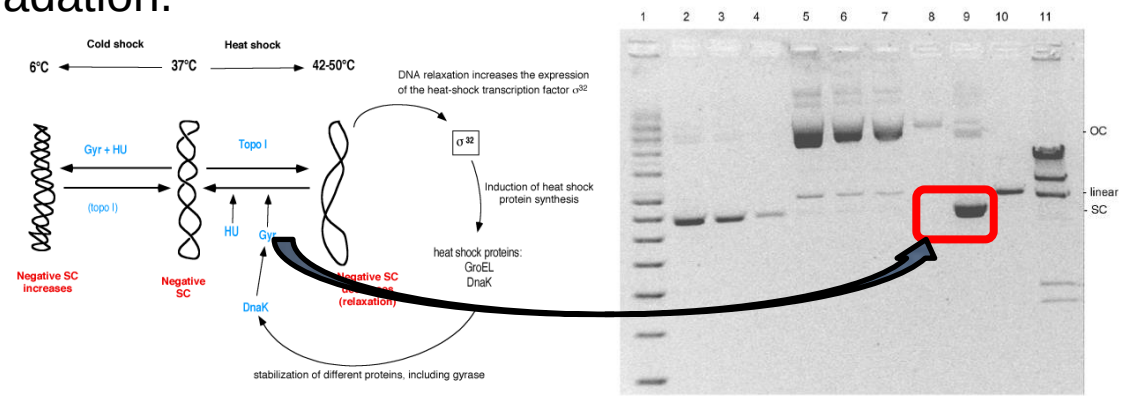
- **Identification of Substances Subject to the Proposed Action**

  To identify known and potential variants of the GTVVs released into the environment.

  - ✓ Identifying and Assessing Potential Environmental Effects
  - ✓ Is the vector virulent, pathogenic, what is known regarding the genetic stability and prevalence of gene exchange in natural populations of the strain or vector?
  - ✓ the product have traits that may give it a selective advantage over natural organisms?
  - ✓ Assessing the magnitude of potential environmental effects
- What is known about the effectiveness of monitoring and mitigation plans?

FDA Environmental Assessment for GMO products

- The release of vector DNA into the environment is detectable by PCR at the injection site and/or in excreta
- Replication competent impurity may cause an active infection in the patient or study participant capable of disseminating to others. ⇒ These variants may arise during manufacture or after product administration because of mutations, or recombination events.
- A super-coiled plasmid may still retain the ability to transfer genetic material (such as antibiotic resistance genes) to other bacteria even after limited degradation.



Levy et al: Quantitation of supercoiled circular content in plasmid DNA solution using fluorescence based method. NAR 28, e57, 2000

Environmental assessment of gene therapy products in USA

Comparison of EA and Biodiversity Assessment

Environmental Risk of Replication Competent Virus and Viral Vector

- Recombinant Oncolytic Virus Vector
- Wild and Attenuated Oncolytic Virus
- Attenuated Viral Vaccine expressing recombinant Antigen (Ebola, MERS antigen etc.)

- Imlygic, recombinant oncolytic HSV-1 virus has a risk on immune-compromised patients, new-born children, pregnant women.
- The sponsor was required to mitigate the risk on transmission of Imlygic to intimate 3rd party and HCP.
- To prevent the 3rd party transmission, the sponsor provides the medication-guide and the education program to patients

Sponsor is required to mitigate the risk for transmission of vectors to 3rd parties in clinical use of gene therapy products (ICH Consideration, viral shedding).
Sponsor should consider the risk of viral vector on various human population.

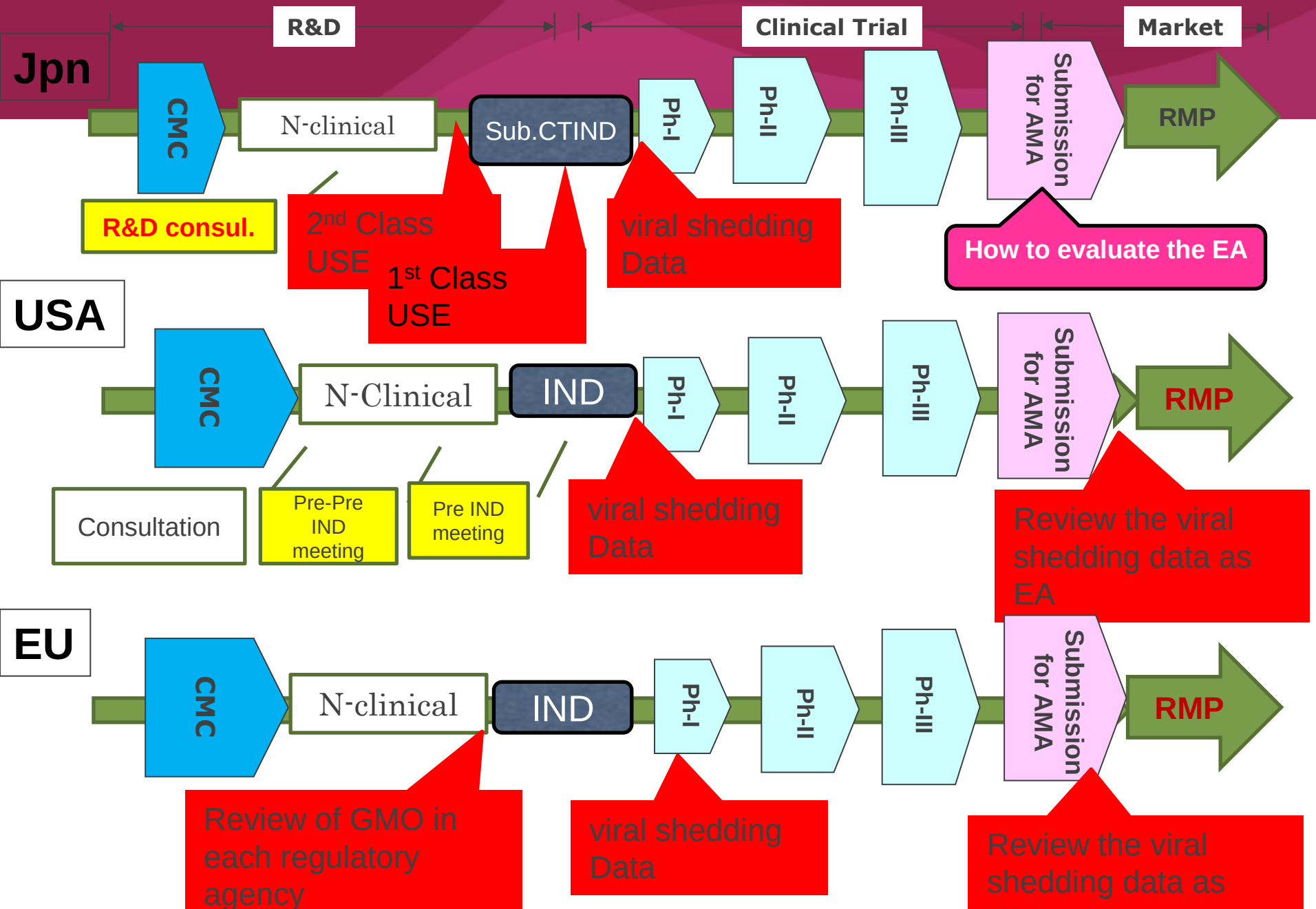
Comparison of GMO Regulation about Gene Therapy Products between EU, USA and Japan

	Japan	USA	EU
Cartagena Protocol	Adopt	No	Adopt
Environment Assessment GL	None	Adopt	Adopt
Focus	Recombinant Virus	Gene Therapy Products include Plasmid	Gene Therapy Products include Plasmid
Review Timing	Before Clinical Study	At Approval for Market Authorization (MA) (except for replication competent virus or etc)	Before Clinical Study by each Regulatory Agency At Approval for MA（EMA）
Viral Shedding	ICH Consideration	Viral Shedding GL	ICH Consideration
Shedding Data		Submit with Approval for MA	Submit with Approval for MA
When collect shedding data	Phase I	Replication Competent Virus: Phase I Non-replication : Phase II	UK：Phase I
Control Pts	In hospital (isolated room)	In or out hospital	In or out hospital

*Cartagena law

✓ Japanese Cartagena Law may correspond to EU and USA environmental Assessment.

Environmental Assessment of GMO in EU, USA and Jpn



Conclusions

- Basically EU and USA perform the environmental assessment for gene therapy products during the review of approval for marketing authorization.
- US FDA considers the replication competent virus vectors may have high risk to immune-compromised population, and requires the sponsor to submit the design for viral shedding studies during clinical trail.
- In Japan, environmental risk of gene therapy product is pre-reviewed onset of clinical trials according to national biodiversity law which have been adopted as part of GMO **risk** assessment .

Thank you !
Any question?

Akebono
Library In KIT