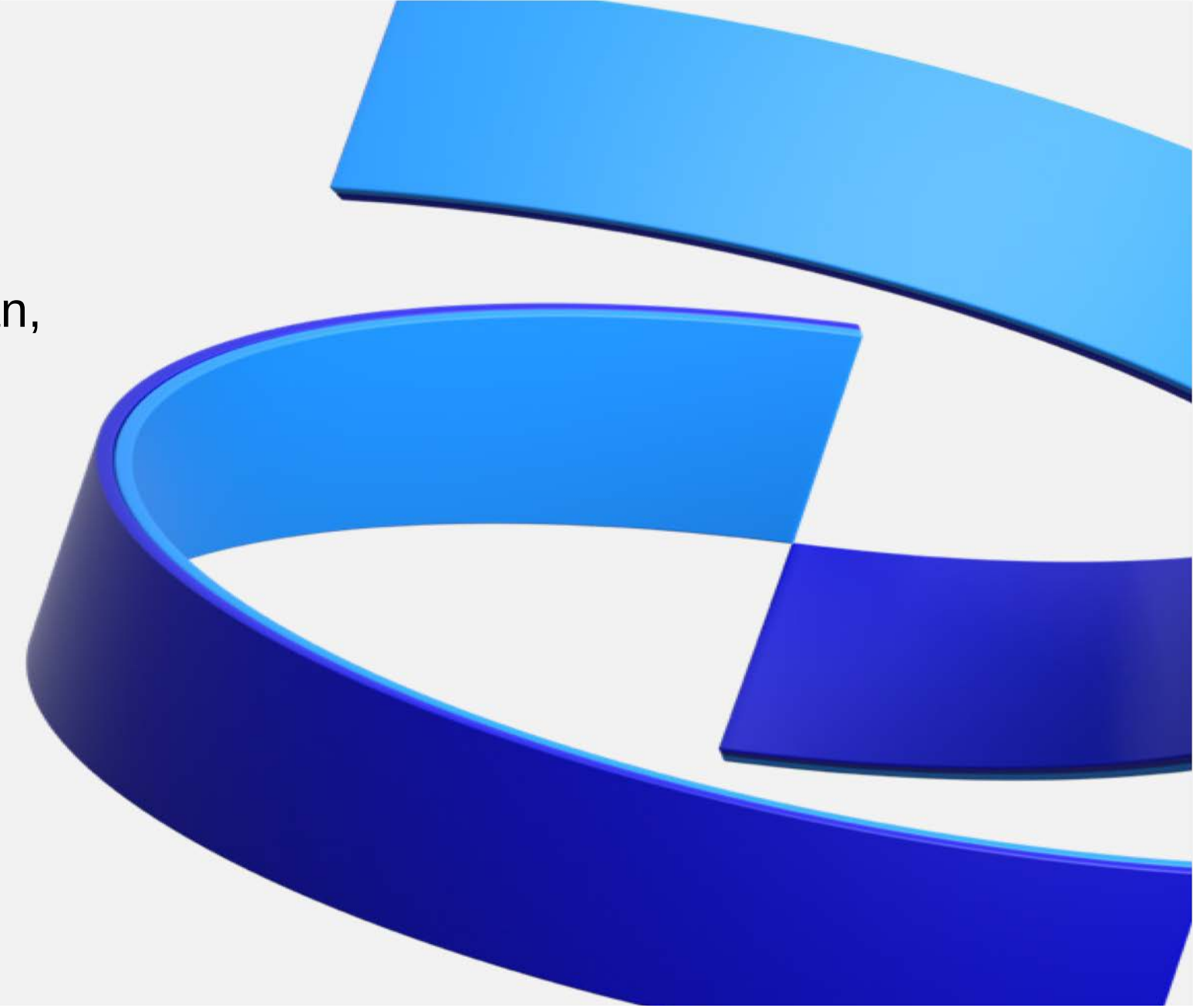
Differences in regulations on gene modified organisms between Japan, Europe, and the United States

Gentaro Tajima, Ph.D.
Regulatory Affairs,
Pfizer R&D Japan

Dec 6, 2022



Disclaimer

- This presentation is intended for discussion purposes only and does not replace independent professional judgment.
- Statements of fact and opinions expressed are those of the individual presenter and, unless expressly stated to the contrary, are not the opinion or position of presenter's employer or affiliating groups.

Agenda

1. Differences in regulations on gene modified organisms (GMOs) between Japan, Europe (EU), and the United States (US)
   - ❑ Regulations and current situation of products containing GMOs in Japan
   - ❑ Regulations and current situation of products containing GMOs in the US
   - ❑ Regulations and current situation of products containing GMOs in the EU
   - ❑ Timing of environmental risk assessment (ERA) and vector shedding studies as regulated by Japan, the EU, and the US
   - ❑ Major regulations and guidelines in each region
2. Proposals to improve GMO regulations
3. Summary of my presentation

Differences in regulations on gene modified organisms (GMOs) between Japan, Europe (EU), and the United States (US)

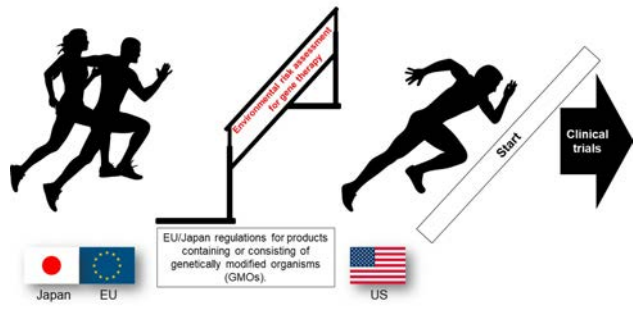
Molecular Therapy
Methods & Clinical Development
Review

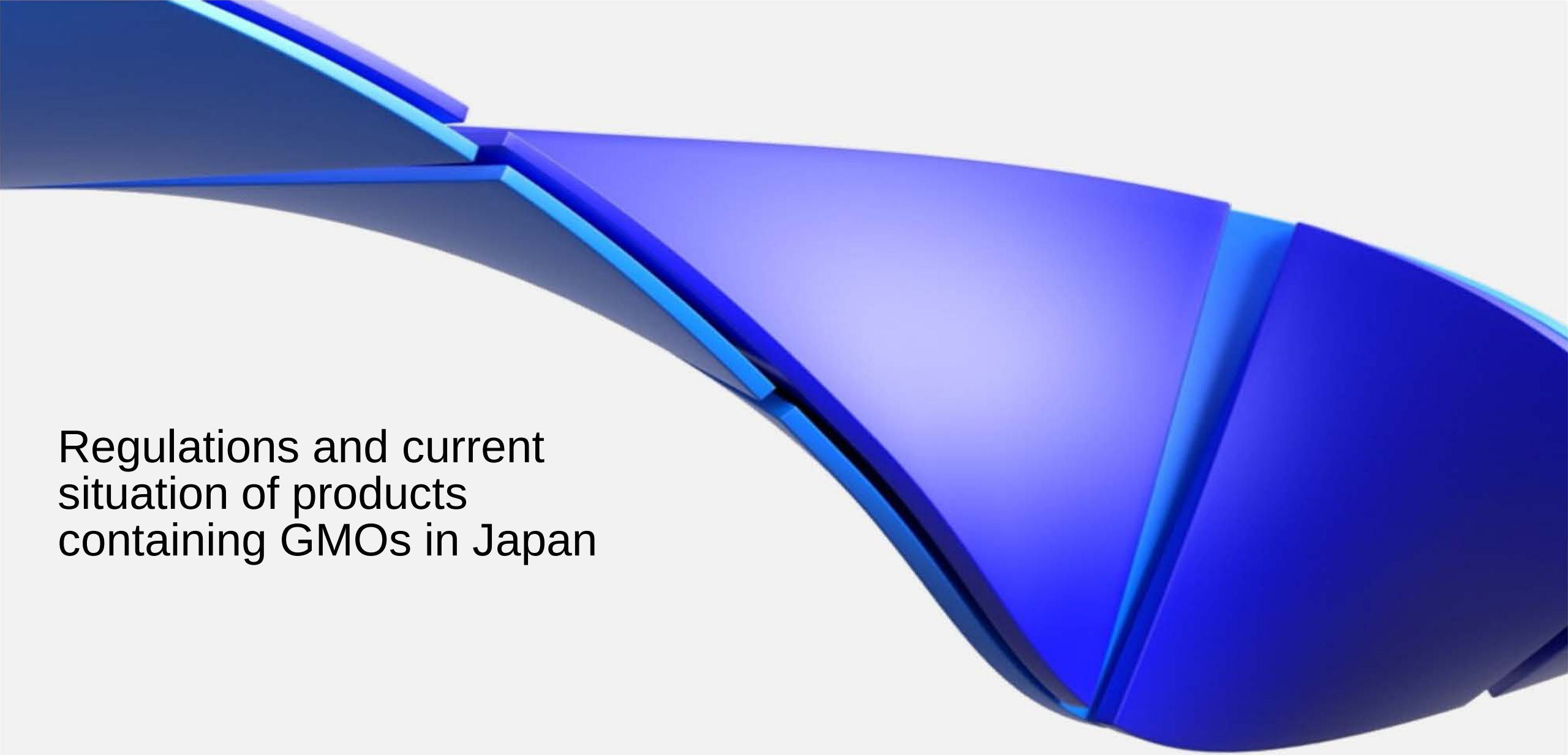
Impact of genetically modified organism requirements on gene therapy development in the EU, Japan, and the US

Gentaro Tajima,[1] Seoan Huh,[2] Natalie Anne Schmidt,[3] Judith C. Macdonald,[4] Tobias Fleischmann,[5] and Keith Merrell Wonnacott[6]

"Japan and EU may be lagging behind in gene therapy development due to additional hurdles related to GMO requirements"

Tajima G, *et al*. Mol. Ther. Methods Clin. Dev. 2022; *26*:74-83.





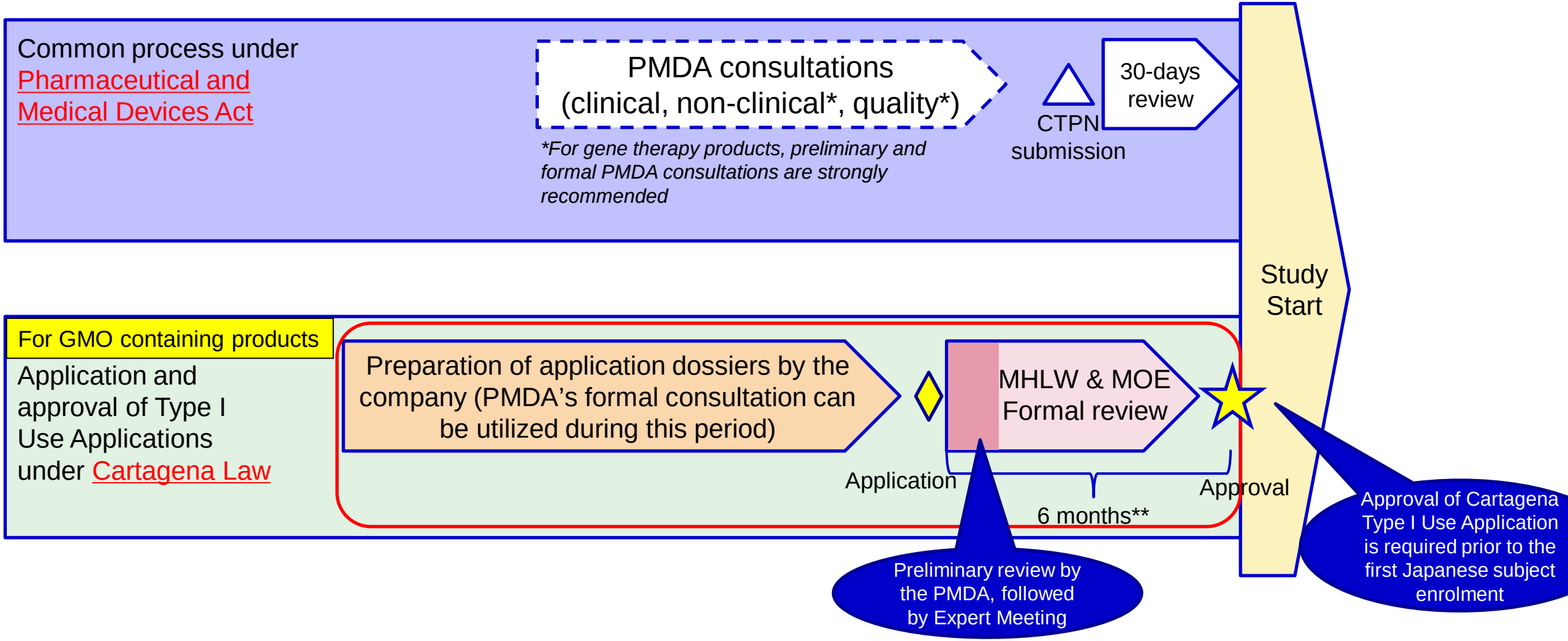
Regulations and current situation of products containing GMOs in Japan

Cartagena Act and GMO

- **Overview of the Cartagena Act**
  - The Cartagena Act is a Japan domestic law, enacted in 2003 to ensure the accurate and smooth implementation of the Cartagena Protocol by taking measures to regulate the use of GMOs, in order to ensure biological diversity through international cooperation. The main target of the regulation is agricultural use of GMOs.
  - There is no mention of "pharmaceutical products" or "regenerative medical products" in the Act. The regulatory requirements based on the Cartagena Act regarding these products are written in the MHLW notifications and other documents.

- **Relationship between Regenerative Medicine Products and the Cartagena Act**
  - When developing "pharmaceutical products" or "regenerative medical products" containing GMOs, it is necessary to comply with the Cartagena Act in addition to the Pharmaceutical and Medical Devices Act.

Regulatory Process to Initiate Clinical Trials for Gene Therapy*



*: The bar lengths do not indicate a time frame, with the exception of 6 months after Cartagena's application.
**: The standard administrative processing time, which does not include the applicant's time.

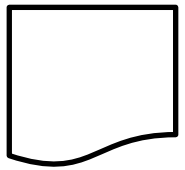
PMDA: Pharmaceuticals and Medical Devices Agency
CTPN: Clinical Trial Plan Notification
GMO: gene modified organism
MHLW: Ministry of Health, Labour and Welfare
MOE: Ministry of the Environment

Cartagena Type I Use Application for clinical trials in Japan

- **Type I Use Applications and Type II Use Applications**
  - The handling of GMOs under the Cartagena Act is classified into Type I Use Applications and Type II Use Applications, and "Type I Use (use without spread prevention measures)" is applied to use in clinical trials.

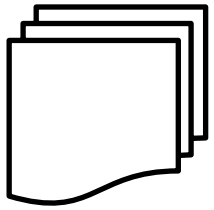
It does not mean that no measures need to be taken with regard to the GMOs to be used if "Type 1 Use" is applied. To minimize the spread of GMOs, it is necessary to specify the method of use of GMOs in the application for approval of Type 1 Use Applications.

Cartagena Type I Use Application submission package



Type I Use Application form (cover letter)

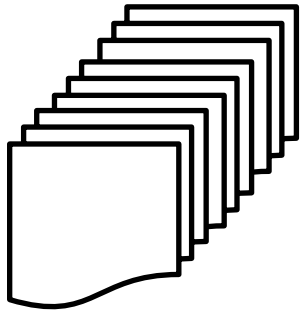
- Handling procedure (Extraction from report)
- 1-2 pages



Biodiversity Impact Assessment Report (≒ ERA)

- About 20 pages

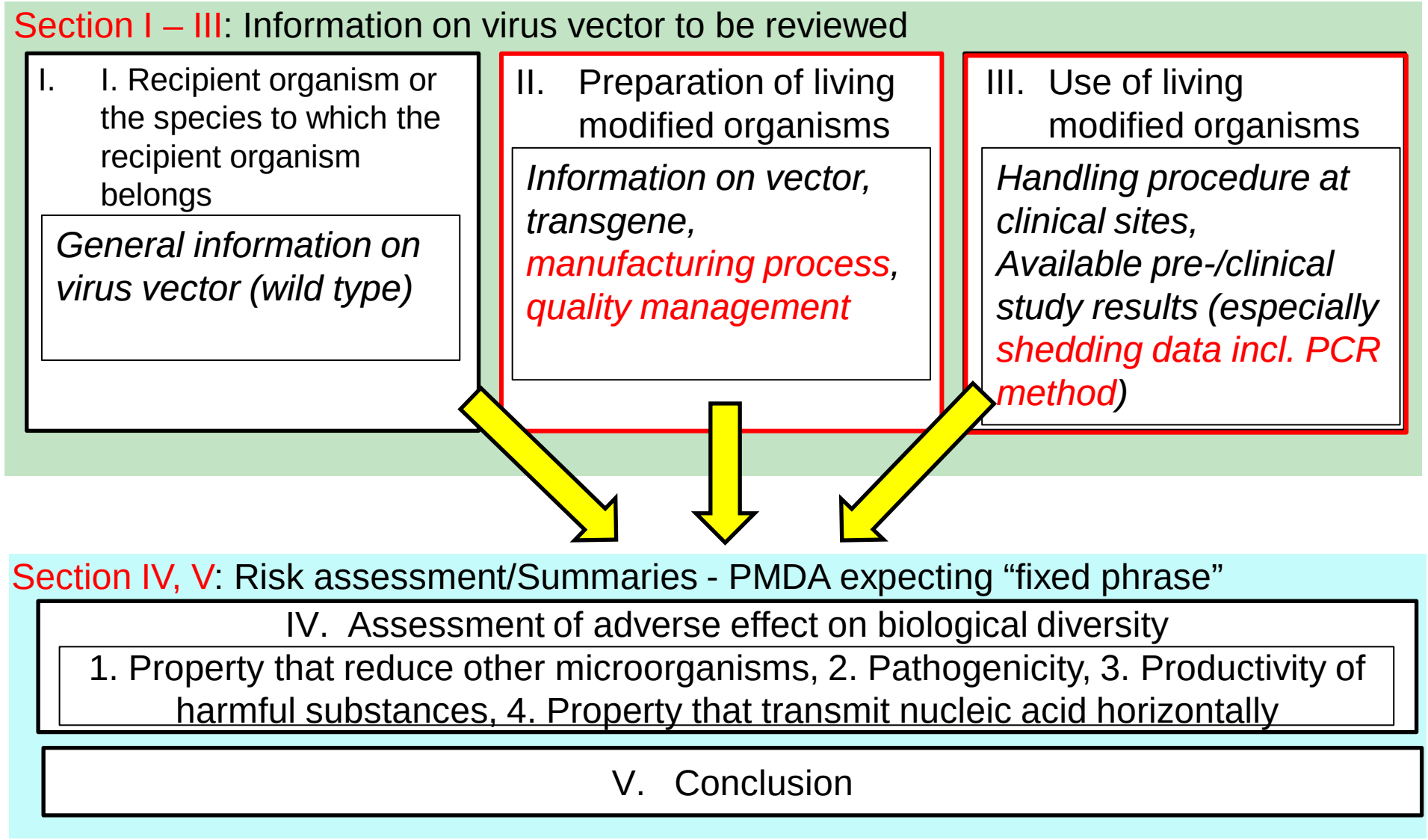
Disclosed to public after approval



Report Attachments

- Less than 100 pages
- Confidential information

Cartagena Biodiversity Impact Assessment Report (≒ ERA)



What does PMDA review?

- **Features of PMDA's review of the Cartagena applications**
  - PMDA requires a wide range of information on clinical and non-clinical, and chemistry, manufacturing, and controls (CMC) per their guidance. Detailed CMC information is specifically required.
  - Viral vector shedding data in humans is crucial. If shedding data cannot be provided to the PMDA at the time of the Cartagena review, more stringent shedding control and patient management, such as hospitalization, tend to be required, especially with novel viral vectors other than AAV, where the PMDA lacks extensive experience and is therefore adopting a conservative approach. However, there is no Japan specific detailed guideline on shedding data requirements.

Cartagena process improvement by the authorities

- **Improvements made by PMDA and MHLW**
  - Apr 2019: Establishment of a new scheme for consultation related to the Cartagena Act
  - Nov 2020: Posting of a mock-up of the Type 1 Use Application Form (for AAV, AdV, HSV)* and Explanatory Notes for Biodiversity Impact Assessment Report on PMDA's website
  - Jun 2021: Posting of a mock-up of Biodiversity Impact Assessment Report for AAV on PMDA's website
  - Sep 2021: Approval timing of Type 1 Use Application changed from before submission of CTPN (similar to CTA and IND)** to before the first subject visit

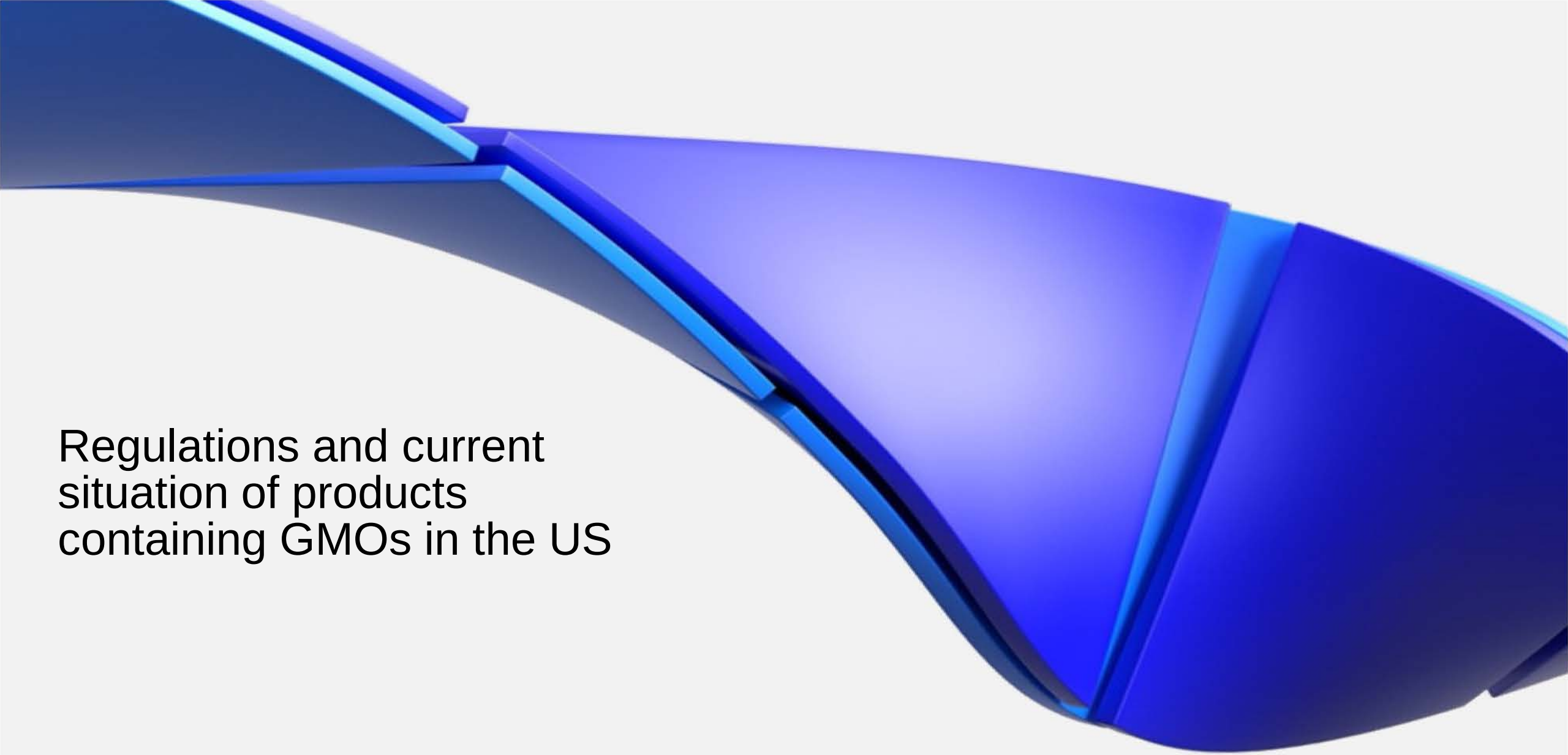
  Etc…

- **Collaboration with a research group from academia and five pharmaceutical trade associations for improvement**
  - An AMED research group***
  - PhRMA Japan, EFPIA Japan, JPMA, FIRM, and Samurai Biotech Association

*: AAV, adeno-associated virus; AdV, adenovirus vector; HSV, herpes simplex virus
**: CTA, clinical trial application; IND, investigational new drug
***: AMED, Japan Agency for Medical Research and Development

Summary of Japan regulations on GMO-containing products

- ERA regulated by the Cartagena Act is mandatory before the start of clinical trials for pharmaceutical/regenerative medicine products containing GMOs.
- Viral vector shedding data in humans is crucial. The method of patient management described in the Type 1 Use Regulations may vary depending on the availability of shedding data. There is no Japan specific guideline on shedding data requirements.
- ERA at the time of application for marketing authorization is not mandatory.
- Regulators, a research group from academia, and five pharmaceutical organizations are working together to improve the Cartagena Act process, and discussions are ongoing for further improvement.



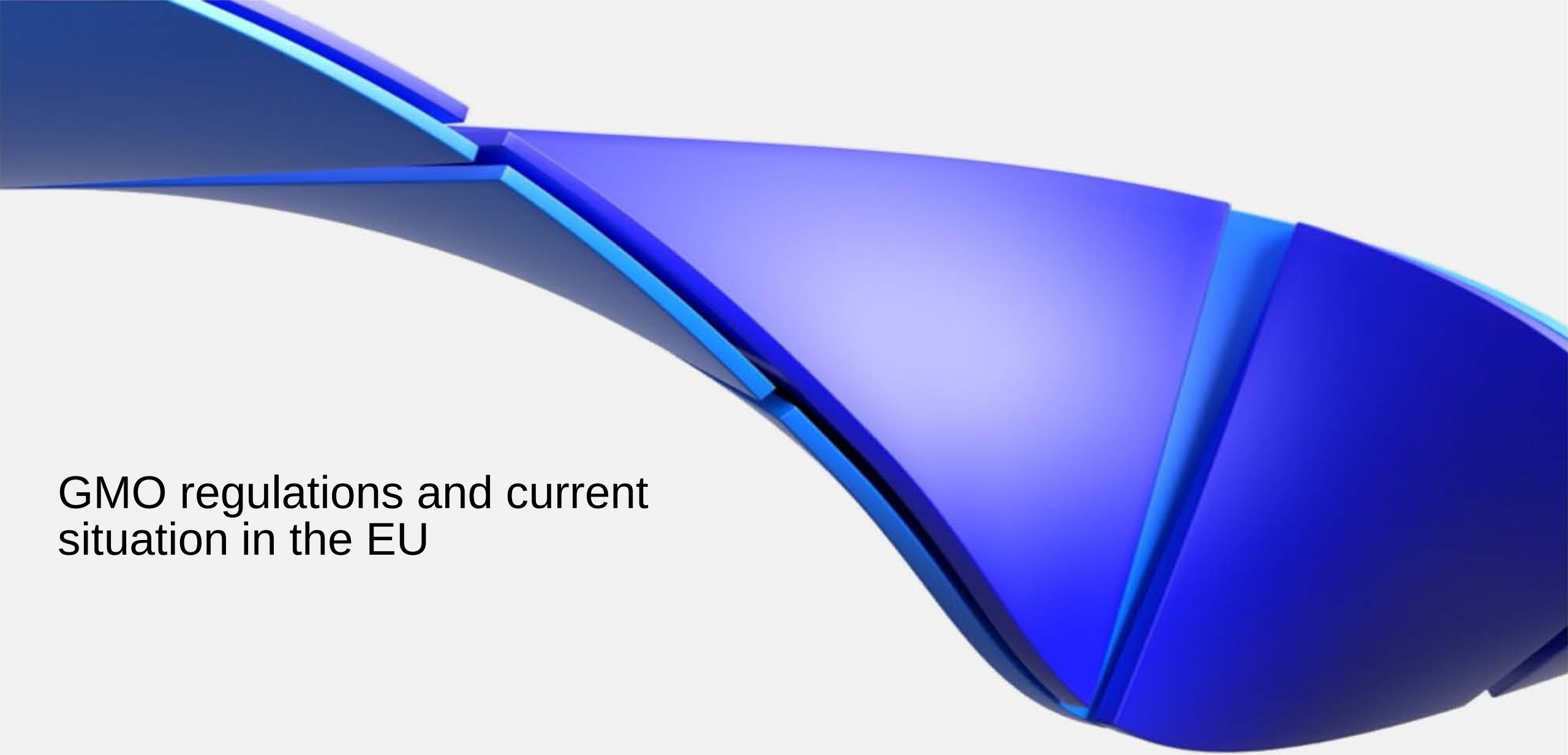
Regulations and current situation of products containing GMOs in the US

Regulations to follow when conducting clinical trials with products containing GMOs in the US

- **Regulation/guidance**
  - The Code of Federal Regulations Title 21 Part 25 (21 CFR Part 25)
  - Determining the need for and content of environmental assessments for gene therapies, vectored vaccines, and related recombinant viral or microbial products - Guidance for Industry
  - Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products - Guidance for Industry
- **Requirements**
  - 21 CFR Part 25 requires an environment risk assessment (ERA) for the approval of any medical products, including gene therapies.
  - An ERA is not required at the start of clinical trials for investigational new drugs, except under special conditions because:
    - The U.S. Food and Drug Administration (FDA) considers it unlikely that novel products will have a significant impact on the environment because products are used in a very limited number of individuals and carefully monitored in the clinical trial setting
  - The 21 CFR Part 25 and FDA guidance provide information on what information is needed for an ERA in a submission of a biologics license application.
  - The FDA does require viral-vector-shedding data to be collected during clinical trials but emphasizes horizontal transmission, not environmental risk.

Summary of US regulations on GMO-containing products

- When conducting clinical trials of pharmaceutical/regenerative medicine products containing GMOs, ERA prior to the start of clinical trials are exempt unless there are special concerns.
- ERA of GMOs at the time of application for marketing authorization is mandatory.
- Human shedding data needs to be collected during clinical trials but emphasizes horizontal transmission, not ERA.



GMO regulations and current situation in the EU

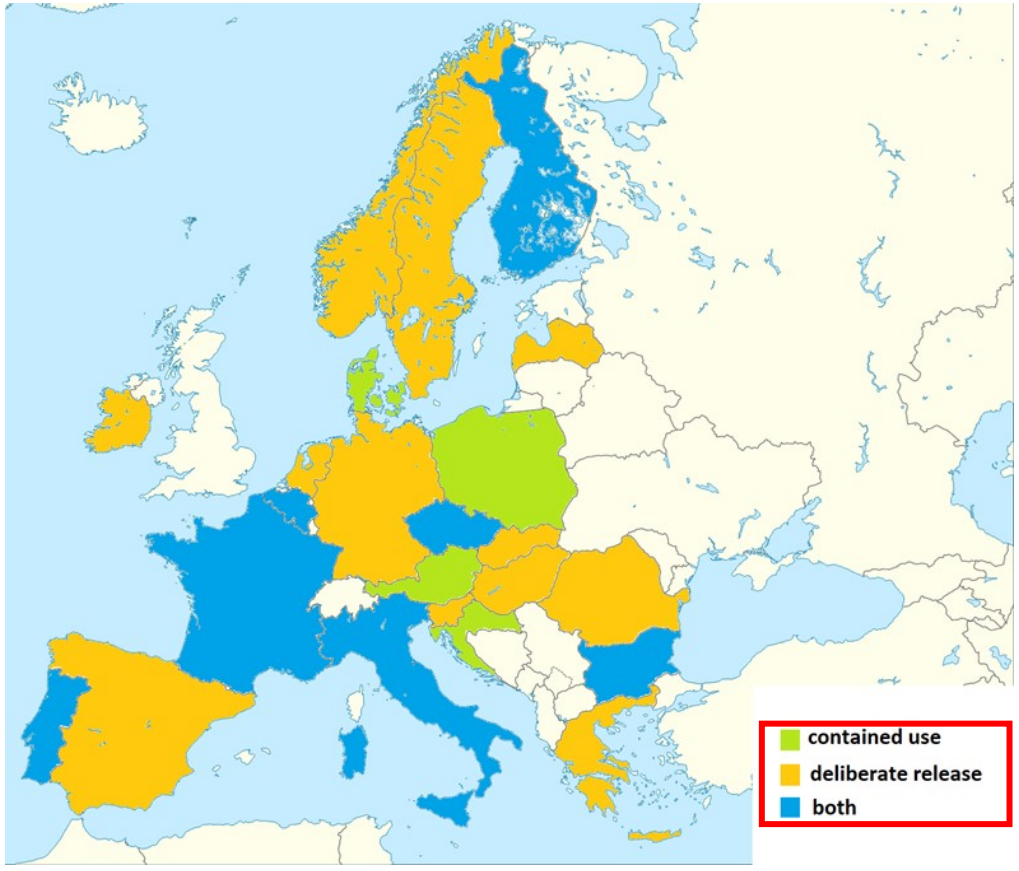
Regulations to follow when conducting clinical trials with products containing GMOs in the EU

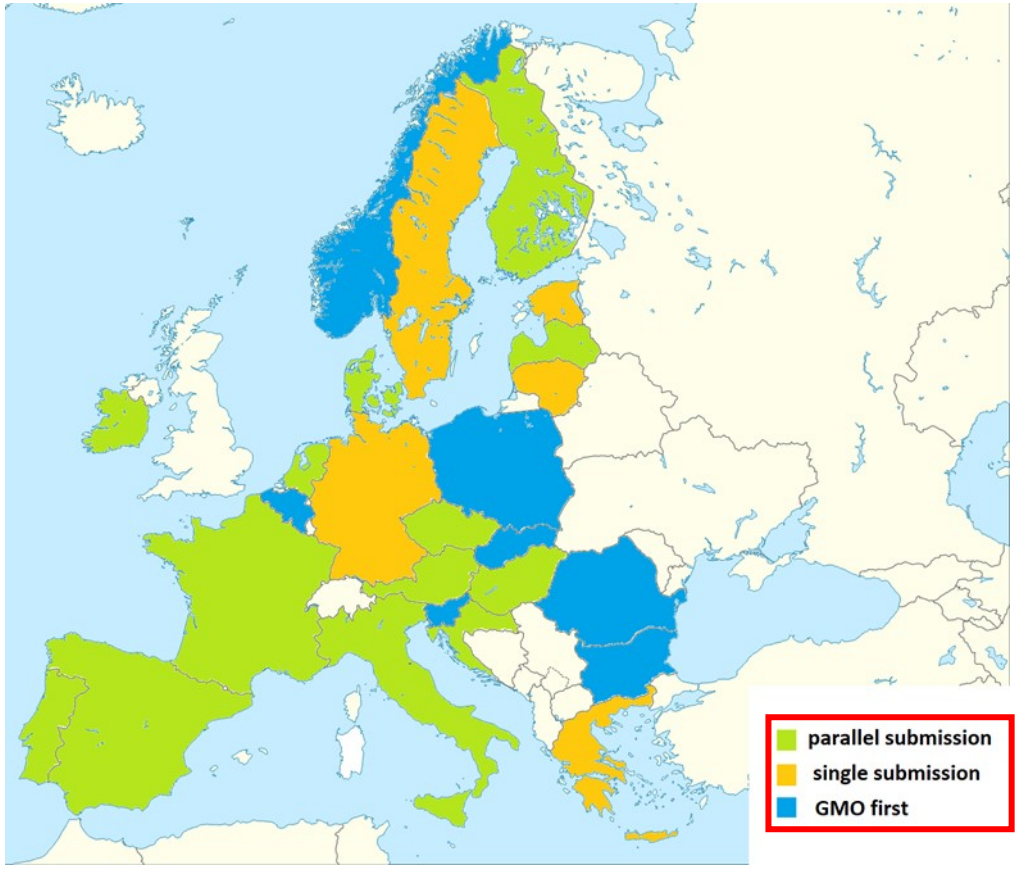
- **Regulation/guidance**
  - Directive 2001/18/EC on Deliberate Release into the environment
    - Directive 2001/18/EC builds on the Cartagena Protocol on Biosafety, an international agreement
  - Directive 2009/41/EC on the Contained Use
  - Guideline on scientific requirements for the environmental risk assessment of gene-therapy medicinal products.

- **Requirements**
  - Both Directives require an ERA approval of any medical products containing GMOs prior to clinical use, including gene therapies.
  - An ERA must be included in the marketing authorization application.
  - Although not mandatory, clinical shedding data or a monitoring plan are expected to be provided

A complex GMO regulatory environment in the EU

- The situation is complicated by the differences in the transposition of these EU directives into national law in the EU member states
  - ❑ Significant variability among EU countries, which is challenging for a sponsor to navigate when executing a pan-EU clinical trial.





Boran T, ASGCT presentation slides, 2021

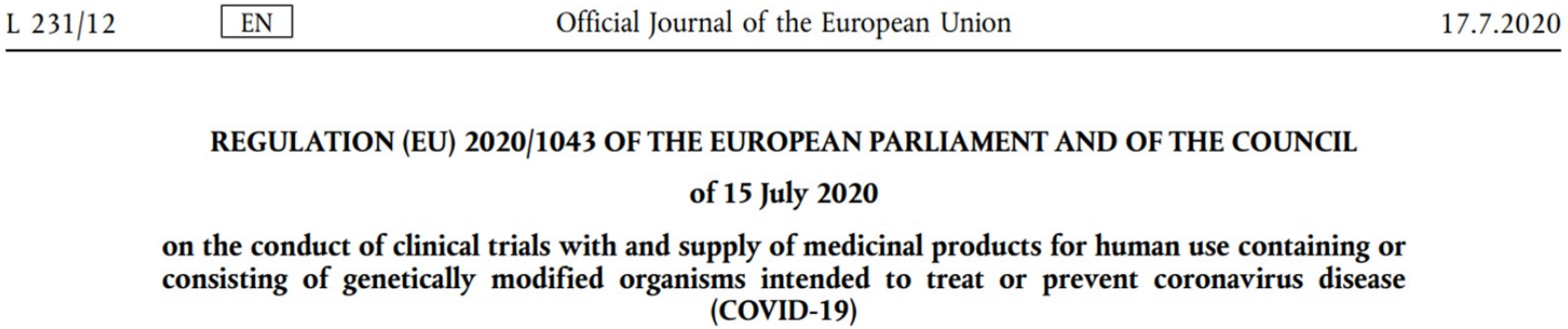
A complex GMO regulatory environment in the EU (cont.)

- Documentation differences between two Directives (Deliberate Release or Contained Use).
- In some member states, the competent authority reviewing the ERA and CTA may be the same (e.g., Germany, Italy, and Sweden), while in other member states, it is different (e.g., France, Spain, and Belgium).
- National agencies have variable review timelines[1], differing languages, and differing views on the classification of products (Deliberate Release or Contained Use).

1) Beattie, S., *et al*. Hum. Gene Ther. 32, 997–1003.

A complex GMO regulatory environment in the EU (cont.)

- The European Commission (EC) and industry have recognized that the clinical development of products containing GMOs is slowed by the current regulatory framework of ERA relating to GMOs.
  - ❑ The recent decision to temporarily exempt coronavirus disease 2019 (COVID-19) treatments from GMO requirements was made to “accelerate the authorization and availability of successful vaccines against COVID-19.”
- The topic of permanent exemption is part of the ongoing discussion on the EC’s pharmaceutical strategy.



L 231/12 EN Official Journal of the European Union 17.7.2020

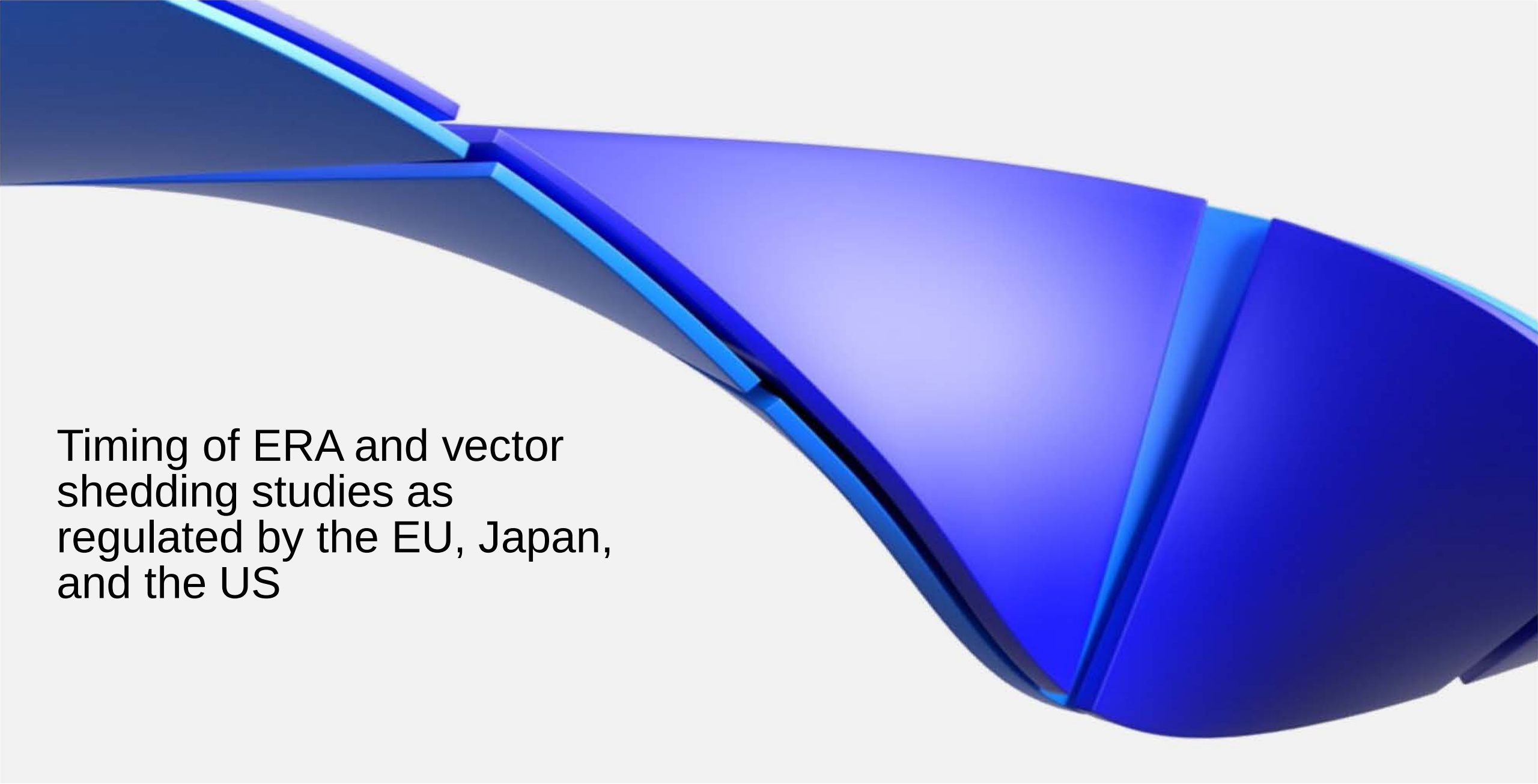
REGULATION (EU) 2020/1043 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 15 July 2020

on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19)

Summary of EU regulations on GMO-containing products

- ERA is mandatory before the start of clinical trials for pharmaceutical/regenerative medicine products containing GMOs.
- Although not mandatory, human shedding data or a monitoring plan are expected to be provided for ERA.
- ERA at the time of application for marketing authorization is mandatory.
- Since there are two regulations, each introduced in different countries based on different interpretations, pharmaceutical companies are required to respond differently even within the EU.
- The EC and the pharmaceutical industry associations continue to discuss ways to improve the process.



Timing of ERA and vector shedding studies as regulated by the EU, Japan, and the US

Differences in the timing of environmental risk assessments and vector-shedding studies as regulated by the EU, Japan, and the US

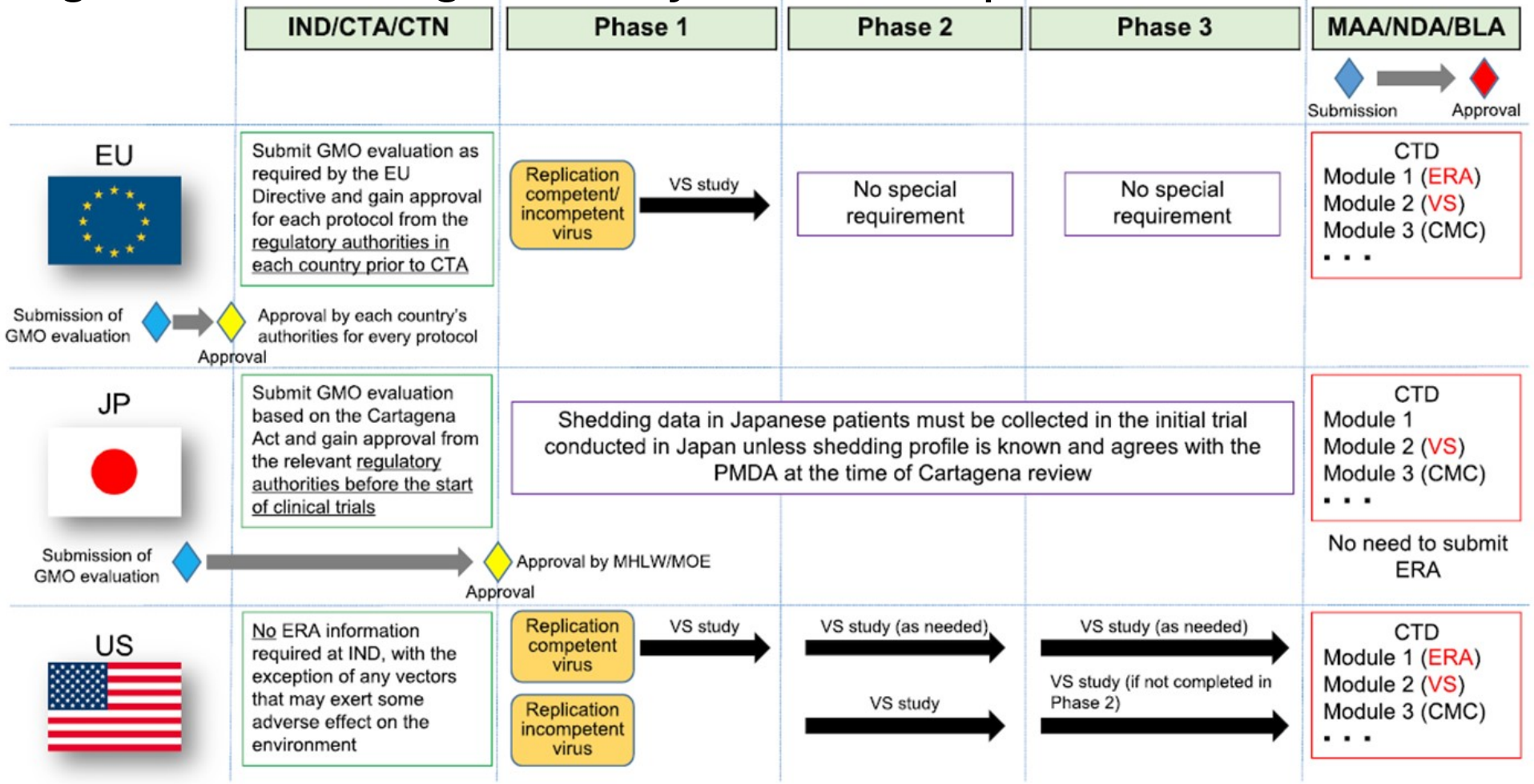
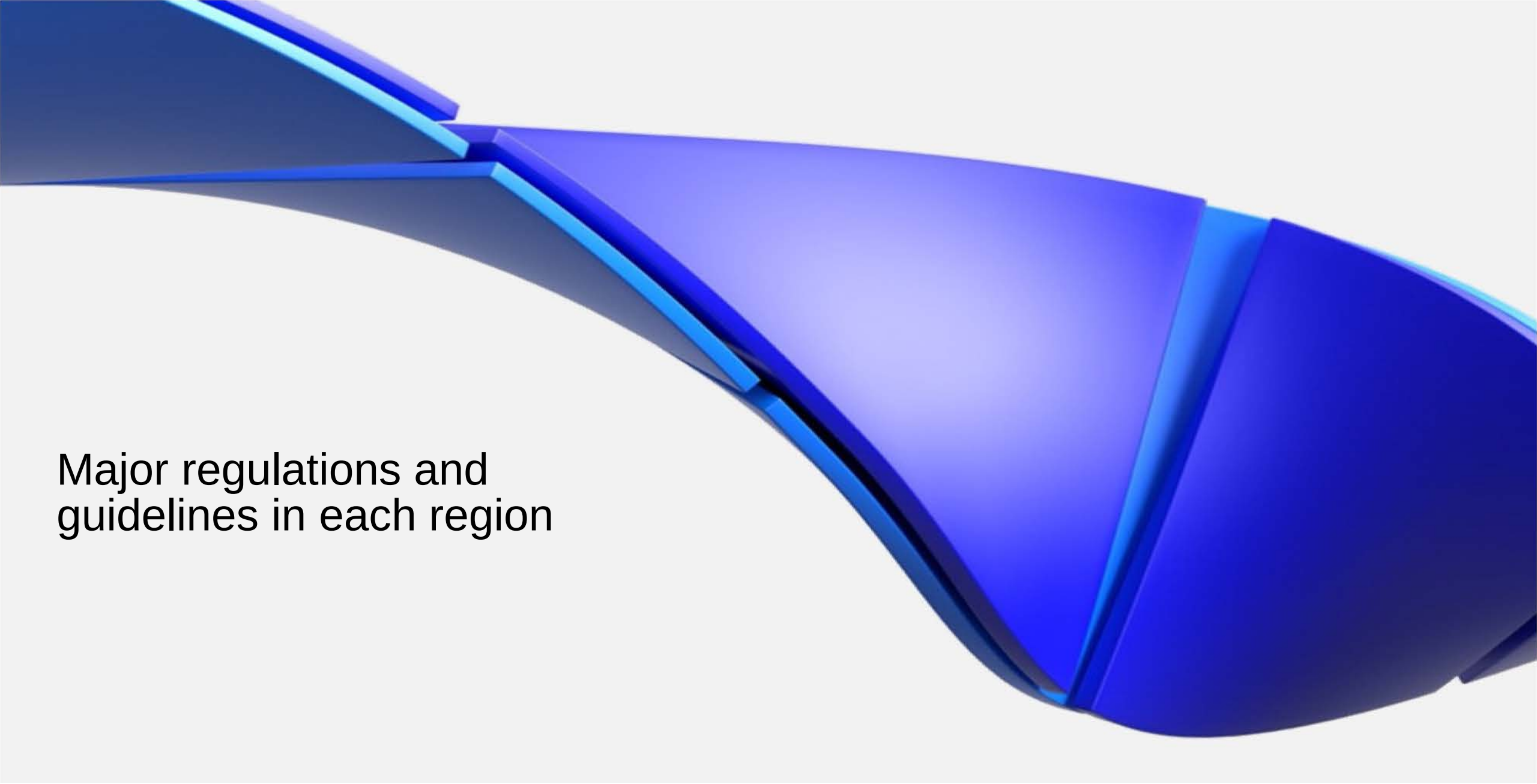


Figure 1. Differences in the timing of environmental risk assessments and vector-shedding studies as regulated by the EU, Japan, and the US

IND, investigational new drug; CTA, clinical trial application; CTN, clinical trial notification; MAA, marketing authorization application; NDA, new drug application; BLA, biologics license application; EU, European Union; GMO, genetically modified organism; VS, vector shedding; ERA, environment risk assessment; CMC, chemistry, manufacturing, and controls; JP, Japan; MHLW, Ministry of Health, Labour and Welfare; MOE, Ministry of the Environment; US, United States.



Major regulations and guidelines in each region

Summary of the major regulations and guidelines for the environmental risk assessment or vector-shedding studies required by the FDA, EU, MHLW regulatory authorities, and the ICH

Table 1. Summary of the major regulations and guidelines for the environmental risk assessment or vector-shedding studies required by the FDA, EU, MHLW regulatory authorities, and the ICH

Region	ICH region	EU		JP		US	
Issuer	ICH	EMA	The European Parliament and the Council of the European Union	MHLW (and five other ministries)	MHLW	FDA	
Relevant document	ICH considerations: General principles to address virus and vector shedding[44]	Guideline on scientific requirements for the ERA of gene therapy medicinal products[45]	EU directive on the deliberate release[9] and EU directive on the contained use of GMOs[10]	Cartagena Act (Type 1 use and Type 2 use for medicinal products containing GMOs)[12]	Points to consider in ERA for approval of the Type 1 use for medicinal products containing GMOs[13]	Design and analysis of shedding studies for gene therapy and oncolytic products[43]	Determining the need for and content of ERA for gene therapies, etc.[17]
Year of issue	2009	2008	2001/2009	2003	2007	2015	2015
Positioning of each document	ICH considerations	EMA guideline based on EU Directive 2001/18/EC	EU directive	Japan local act	MHLW notification based on the Cartagena Act	FDA Guidance for Industry	FDA Guidance for Industry
Description of ERA for GMOs	NO	YES	YES	YES	YES	NO	YES
Description of requirements for vector shedding	YES	NO	NO	NO	YES	YES	NO
Description of timing of vector shedding studies	NO	YES	NO	NO	NO	YES	NO
Description of timing of submission of shedding data or ERA data	NO	YES	YES	NO	YES (for ERA)/NO (for shedding data)	YES	YES

ICH, International Council for Harmonization of the Technical Requirements for Pharmaceuticals for Human Use; EU, European Union; JP, Japan; US, United States; EMA, European Medicines Agency; MHLW, Ministry of Health, Labour and Welfare; FDA, US Food and Drug Administration; ERA, environmental risk assessment; GMO, genetically modified organism.

Proposals to improve GMO regulations to facilitate international development

Proposal for future improvements

- Given the growing trend of simultaneous global drug development, excessive GMO requirements by some countries may prevent the inclusion of these countries in global studies, resulting in prolonged development timelines and delays in the availability of advanced therapies for diseases with unmet medical needs.

- The long-term goal in both the EU and Japan should be to consolidate national oversight under medicinal-product regulations and exempt medicinal products from additional GMO requirements.
- Despite positive changes made by the authorities in both the EU and Japan, there remains a significant amount that can be done to improve existing processes. There are three key challenges imposed by the GMO requirements, and each is a potential area for improvement:
  - ❑ Documentation: The number, type, and length of documentation required vary widely and are largely duplicative with the information included in medicinal-product dossiers.
  - ❑ Data: There is great disparity in the kinds of data needed and the point at which data are needed during the development of a GMO product.
  - ❑ Timelines: The time required to gain regulatory approval for GMO utilization can be significant and prohibitive for a country's inclusion in a multi-regional clinical trial

Summary of my presentation

Summary

- The GMO regulations were largely developed out of environmental concerns regarding GMOs for agricultural use.
- In Japan and the EU, an ERA is required prior to the start of clinical trials for pharmaceutical/regenerative medicine products containing GMOs (but the situation differs). In the US, it is exempted unless there are special concerns.
- In the EU and the US, an ERA is mandatory when applying for marketing authorization of a pharmaceutical/regenerative medicine product containing GMOs. Not required in Japan.
- There is no harmonization in Japan, the US, and the EU regarding the requirements for ERA of GMOs and the documents to be submitted.
- PMDA considers human shedding data to be important. PMDA's review has several characteristics, such as managing patients in a private room depending on the type of vector.
- Both Japan and the EU are improving their regulatory process for ERA of GMOs prior to the start of clinical trials, but the time gap between Japan and the US has not been made up, and pharmaceutical companies in both regions are requesting further process improvements from the regulatory authorities.

Thank You