Implementation of 3Rs to quality control of biologicals and lot release tests in Japan

AFSA-IABS Conference “Animal testing replacement for vaccines: A One Health View: global outlook and future strategy”

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Bangkok, Thailand

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Framework for implementation of 3Rs into tests for quality control and lot release in Japan

Step 1: accumulation of sufficient data for removal or modification of animal tests, in many cases by collaborative studies with manufacturers.

Step 2: proposal for the removal/modification of tests to the internal committee of NCL=NIID (now JIHS).

Step 3: proposal to the superior committee that includes the NCL and NRA=MHLW (Ministry of Health, Labour and Welfare), PMDA (Pharmaceuticals and Medical Devices Agency).

Step 4: approval and public notice in the Official Gazette.

Current Status of Animal Tests in Japan

Diphtheria-pertussis-tetanus combined vaccine

- Potency test by diphtheria toxin challenge in mice } diphtheria
- Detoxification test in rabbits
- Potency test by tetanus toxin challenge in mice } tetanus
- Detoxification test in guinea pigs
- Potency test in mice } pertussis
- Lethal histamine sensitization toxicity assay in mice

Inactivated polio vaccine (Sabin)

- D-Antigen ELISA established

Japanese encephalitis vaccine

- Potency test by Lethal challenge in mice
- Inactivation in mice

Rabies vaccine

- Potency test by Lethal challenge in mice
- Inactivation in mice

Rubella vaccine (bulk material)

- Marker test in guinea pigs

Hepatitis A vaccine

- Antigen ELISA established

Hepatitis B vaccine

- Replaced by antigen ELISA (Dec. 2021)

General tests

- Abnormal Toxicity Test in guinea pigs
- Endotoxin test

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Replacement in progress

Hepatitis B vaccine

- Replaced by antigen ELISA (Dec. 2021)

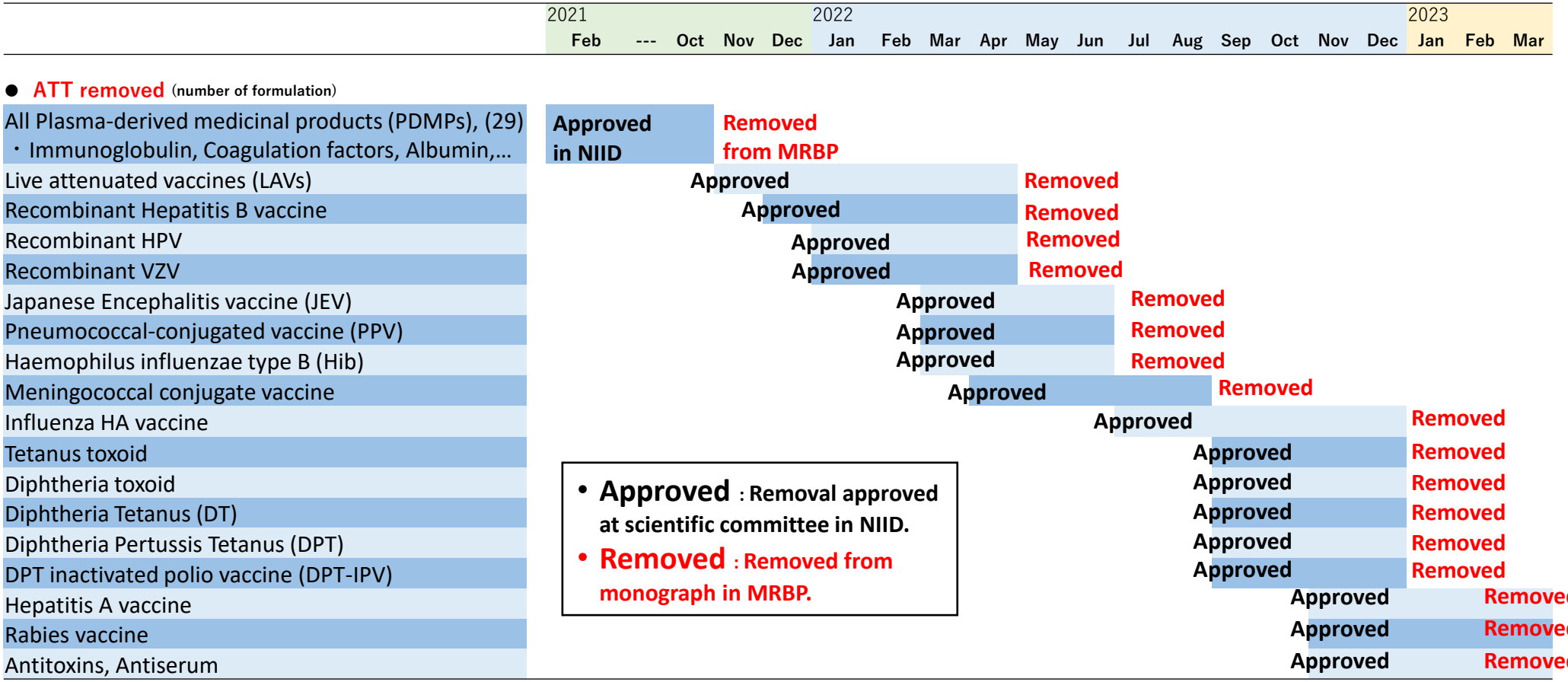
Rubella vaccine (bulk material)

- Marker test in guinea pigs

General tests

- Endotoxin test

Recent progress of ATT removal from MRBP in 2021-2023



ATT has been **removed from all products** until March 2023.

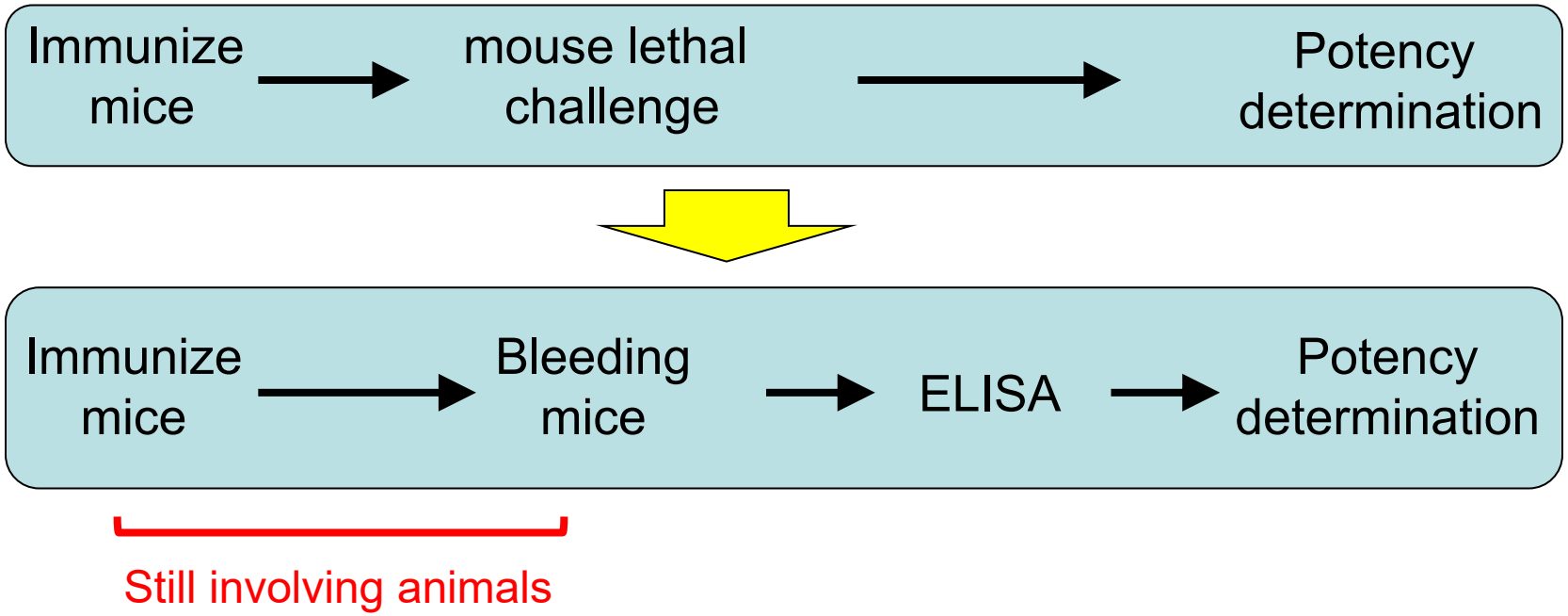
Rabies

- Rabies-free country but needs vaccine (as travelers' vaccine etc).
- Potency test and Inactivation test mandatory by Japanese Minimum Requirement
- NIH method (mouse intracerebral challenge) -> need for replacement to animal-free
- Participated in EDQM BSP148 (antigen ELISA) Phase 1-3
- Effort for improvement and implementation in progress

Japanese encephalitis

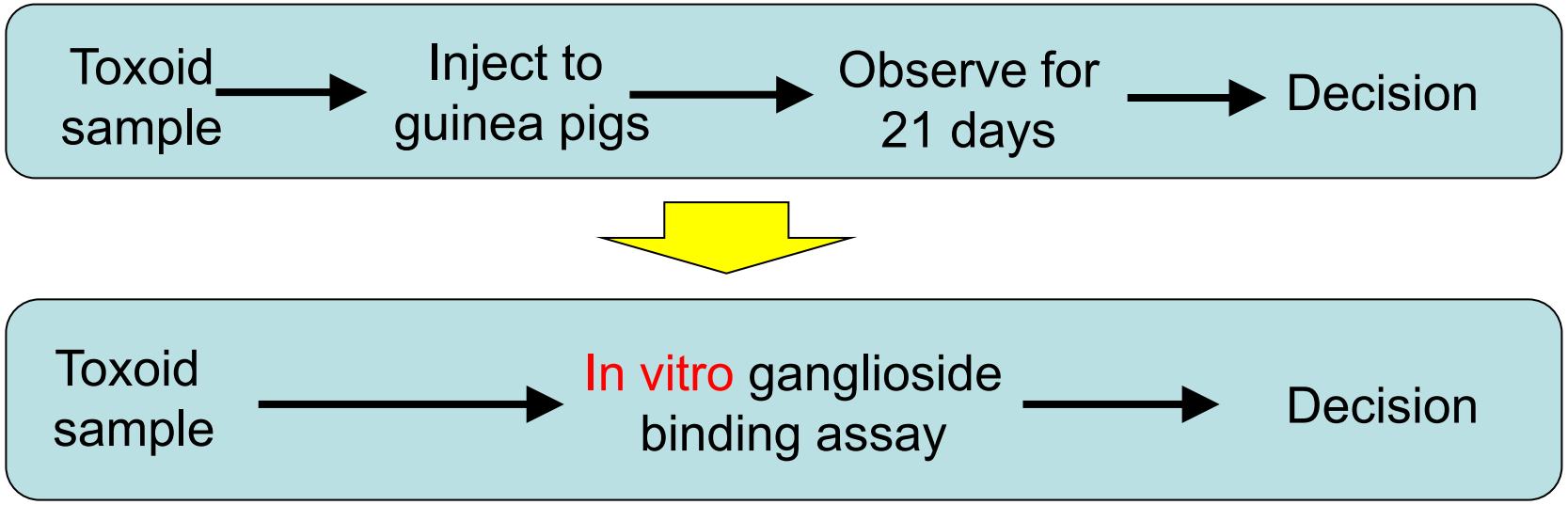
- In the national assay for the Japanese encephalitis vaccine, the potency test and the inactivated test are conducted using the mouse model.
- The introduction of the simpler antigen ELISA test method as an alternative to the current potency test method is being considered.

Tetanus toxoid potency test



- Validation study with manufacturers completed
- Revising Japanese Minimum Requirement in progress

Tetanus toxoid detoxification test

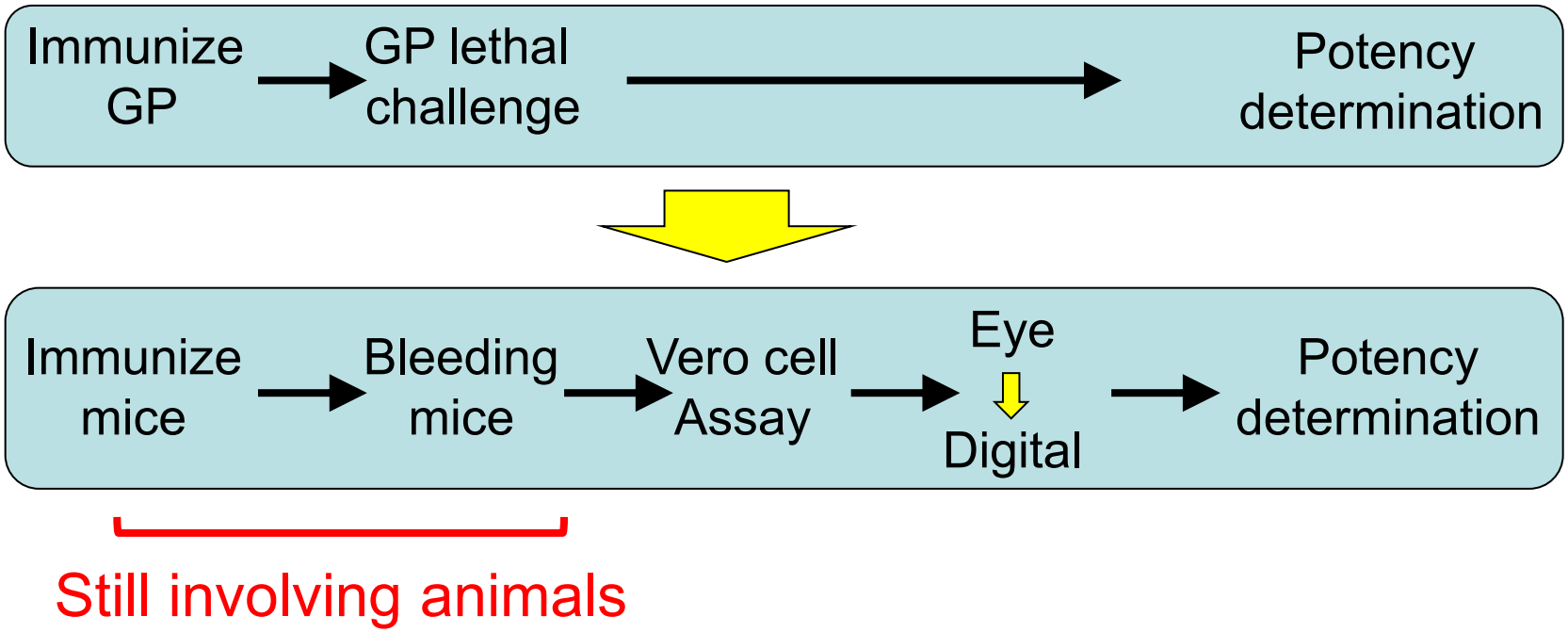


Animal-free

(Tanoue et al. *Toxins (Basel)*, 2025. 17:500.)

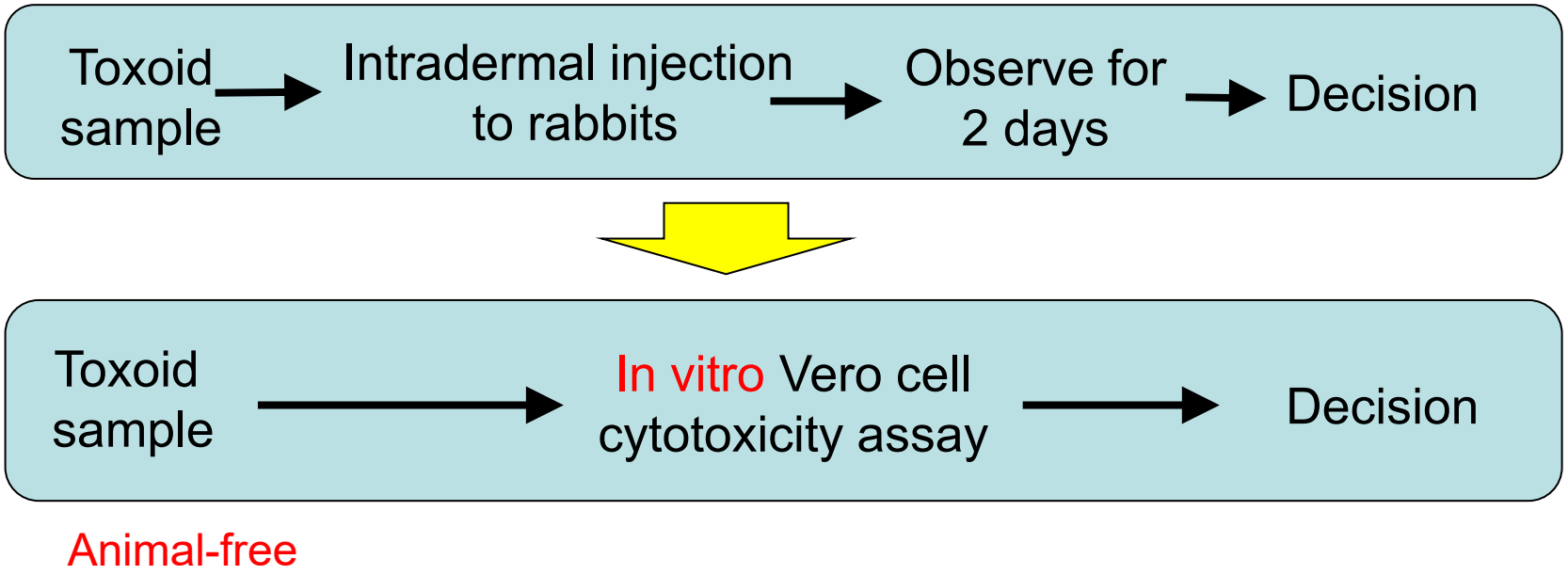
Further study ongoing

Diphtheria toxoid potency test



Already implemented, in use (QC and lot release) for more than 20 years

Diphtheria toxoid detoxification test



Study ongoing

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Thank you for your attention

JIHS

Japan Institute for Health Security