



Inno4Vac Final Stakeholder Meeting | September 28-29, 2026 in Leiden, Netherlands

Dutch GMO regulation and CHIM studies

Reverse Genetics-Derived Viruses: Regulatory Challenges and Opportunities

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Contents of the Presentation

- Clinical Isolates versus reverse genetics derived viruses
- Dutch GMO framework for Deliberate Release
- Authorization pathway for CHIM studies
- International regulatory comparison

CHIM studies with clinical isolates vs RG strains

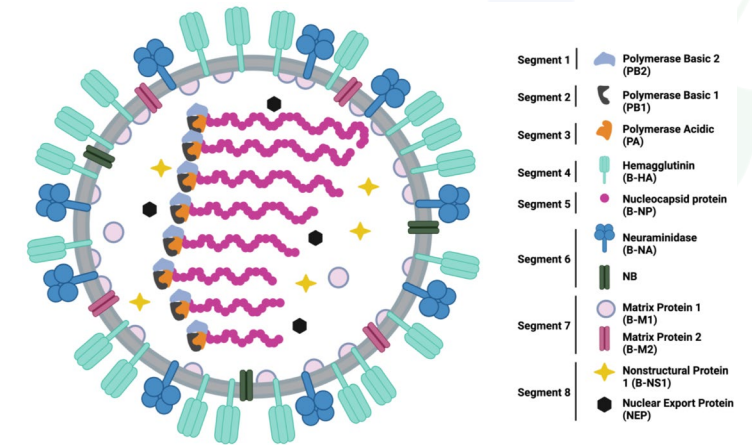
Controlled Human Infection Model

- Supports vaccine and antiviral development
- Improves understanding of pathogenesis and correlates of protection
- Utilize well-characterized challenge strains
- Can employ:
 - Clinical isolates
 - Reverse genetics strains
- Manufacturing approach directly influences regulatory requirements



CHIM studies with clinical isolates vs RG strains

- Clinical isolates:
 - Naturally circulating strains
 - Variable level of characterization
 - Potential genetic heterogeneity
 - Presence of adventitious viruses possible
- Reverse genetics viruses:
 - Sequence-defined and reconstructed from cloned genetic material
 - Complete characterization/known sequence
 - High reproducibility and design flexibility
 - Enhanced standardization and manufacturing consistency



Clinical Isolate and RG virus CHIM Studies

- Clinical isolates
 - Lower regulatory burden. Ethical review only
 - Limited environmental risk mitigation requirements
 - Primary focus on participant safety and product quality
- RG viruses
 - GMO review in addition to ethical review
 - Case-by-case classification
 - Increased regulatory oversight
 - Environmental Safety Officer
 - Extensive mitigation measures
 - Strong emphasis on environmental risk



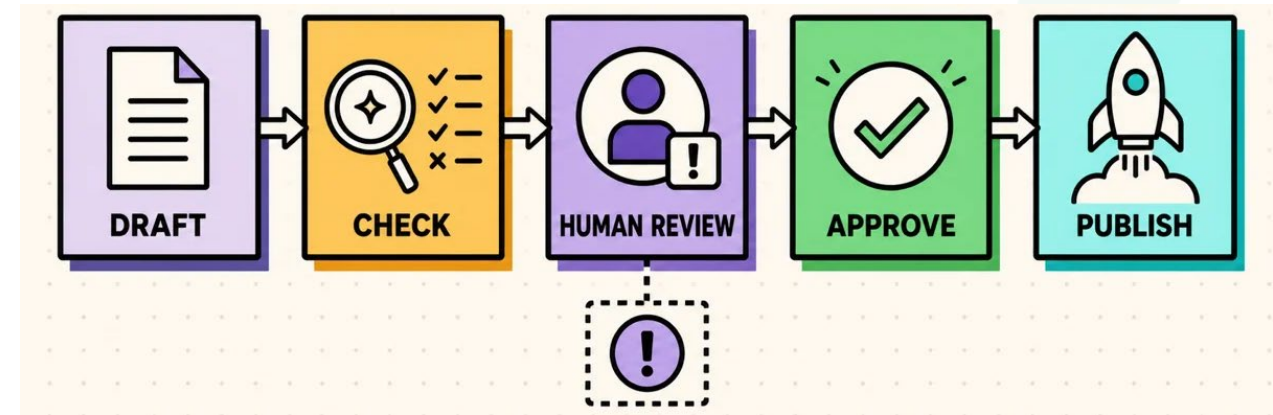
Dutch Regulatory Framework

- Clinical isolates
 - Ethical review by accredited Medical Ethics Committee
- Reverse genetic viruses
 - Dual review system
 - Clinical Evaluation
 - CTIS and CCMO review
 - Environmental Evaluation
 - Ministry of Infrastructure & Water Management
 - GMO Office
 - Independent COGEM advice



Dutch Authorisation Pathway

- Clinical Trial authorization
 - CTIS submission
 - Clinical assessment
 - Trial authorization
- GMO dossier:
 - Environmental Risk Assessment (ERA)
 - COGEM review
 - Public consultation
 - Authorization for the study-> Environmental GMO permit decision

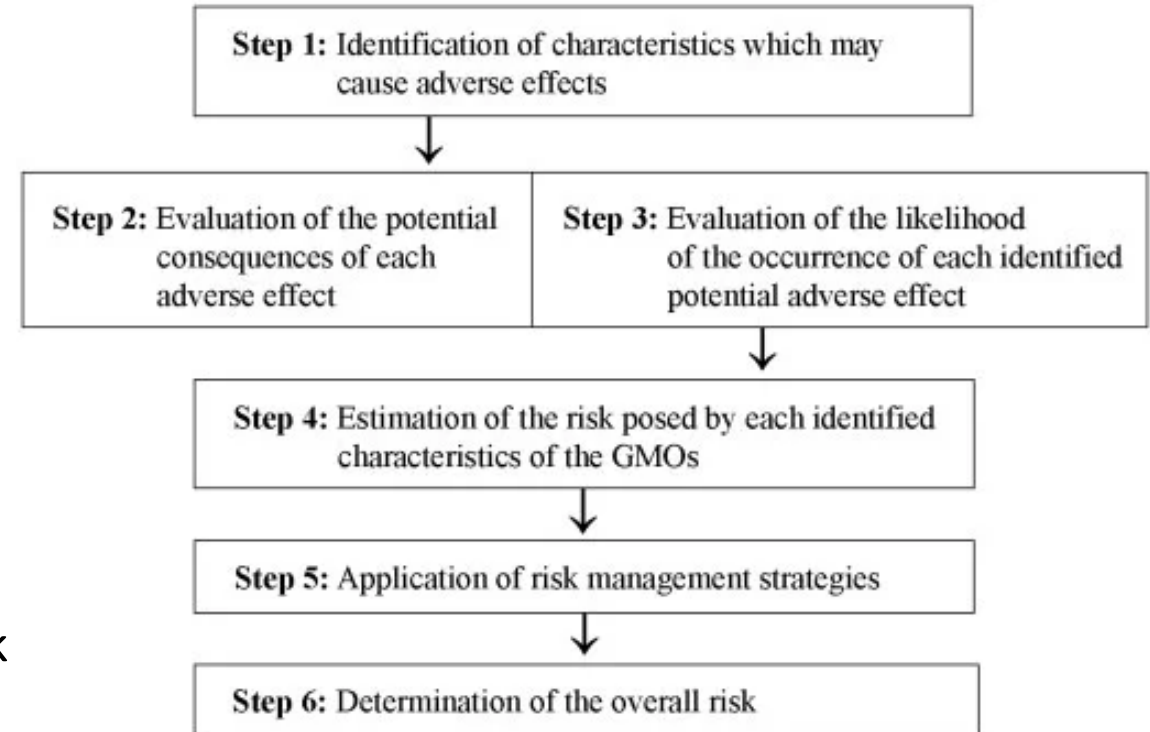


Additional Dutch Requirements for RG CHIM agents

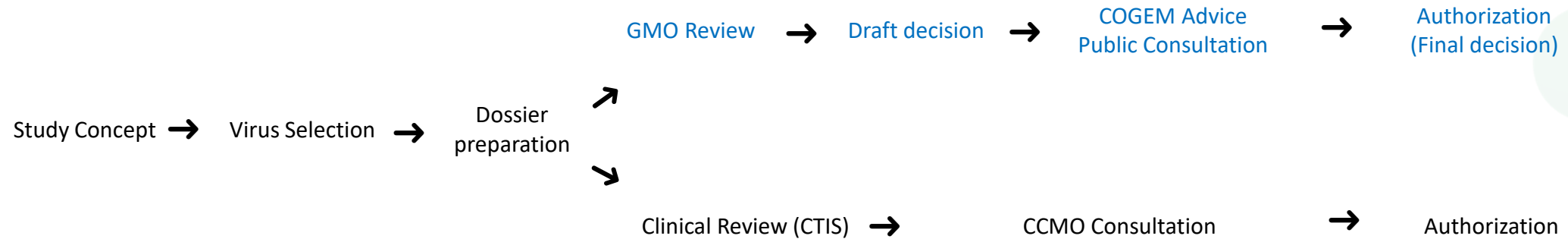
- Recombinant nucleic acid technology generally GMO assessment.
- Classification depends on:
 - Viral construct
 - Development technology
 - Regulatory interpretation.
- the Netherlands only accept clinical studies with negligible environmental risk
- GMO dossier:
 - Agent description
 - Manufacturing process
 - Molecular characterization
 - Comparative risk assessment with wild-type agent
 - Environmental Risk Assessment (ERA) package
 - Extensive amount of mitigation measures
 - Waste management strategy

Environmental Risk Assessment

- Important features in the ERA:
 - Viral shedding
 - Transmission potential
 - Environmental persistence
 - Environmental exposure
 - Ecological impact
 - Risk mitigation measures
- Outcome:
 - Demonstration of negligible environmental risk



Dutch Approval Pathway for Reverse genetics CHIM Studies



GMO pathway (minimum):

Stage	Duration
Dossier preparation	20-60 days
Draft decision	42 days
COGEM review + Public consultation	42 days (+7 days)
Final decision	42 days

- Typical minimum timeline: 150 – 190 days



Regulatory Complexity Comparison

Relative Complexity of regulatory requirements for reverse genetics-derived CHIM studies

Regulatory Element	NL	EU	UK	USA
Clinical Trial Approval	●	●	●	●
GMO Assessment	●	●	●	●
Environmental Risk Assessment	●	●	●	●
Public Consultation	●	●	●	●
Documentation Burden	●	●	●	●
Timeline Impact	●	●	●	●
Overall Complexity	●	●	●	●

Red = High complexity; Orange = Medium; Green = Low

International Regulatory Comparison

The regulatory treatment of reverse genetics-derived viruses varies considerable between jurisdictions

Aspect	NL	EU	UK	USA
Clinical approval	CCMO+CTIS	CTIS	MHRA	FDA
GMO review (ERA)	Yes	Usually	Often	Generally, No
Timeline	High	Med-High	Medium	Low
Burden	Highest	Variable	Moderate	Lowest

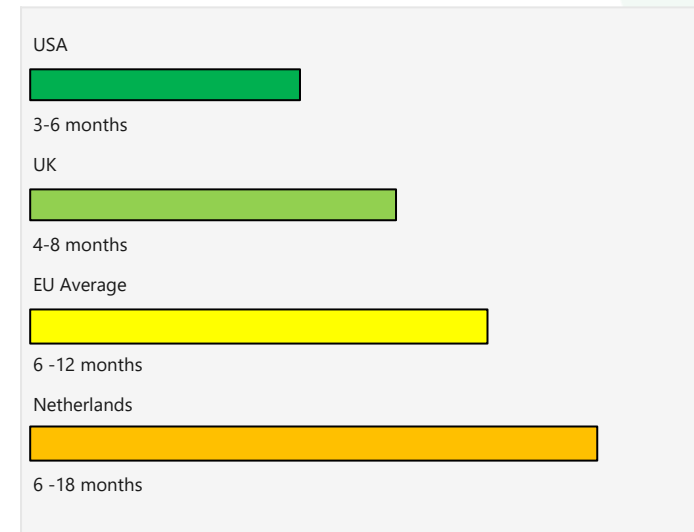
- UK, USA do not treat RG viruses as GMOs in clinical studies

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Timelines



- UK, USA do not treat RG viruses as GMOs in clinical studies

Centre for Human Drug Research RG H3N2 CHIM study

- Preparing the application: ~ 3 months (incl. revisions)
- Submission date: 14 May 2024
- 5 revision rounds required before dossier acceptance
- Draft decision published: 25 April 2025
- COGEM review And public consultation
- Final authorization published on 23 June 2025
- Total timeline:
- Approximately 15 months

Beschikking op de vergunningaanvraag van Centre for Human Drug Research te Leiden, voor introductie in het milieu van genetisch gemodificeerde organismen.

Vergunningsaanvraag

Op 23 juni 2025 is door de Minister van Infrastructuur en Waterstaat vergunning verleend met kenmerk IM-MV 24-004_001 aan Centre for Human Drug Research voor de introductie in het milieu van genetisch gemodificeerde organismen krachtens het Besluit genetisch gemodificeerde organismen milieubeheer 2013.

Op 14 mei 2024 heeft Centre for Human Drug Research hiertoe een strekkende aanvraag ingediend.

De aanvraag heeft betrekking op klinische studies waarbij proefpersonen worden blootgesteld aan een genetisch gemodificeerd griepvirus om onderzoek te doen naar de effectiviteit van antivirale medicatie en vaccins tegen griep.

De werkzaamheden zijn voorgenomen plaats te vinden in de gemeente Leiden.

Lessons Learned from the CHDR H3N2 study

Final public dossier:

- 45 pages in total
- 4 pages additional measures (clinical trial subject and CHDR test facility)
- 11 pages Environmental Risk Assessment (ERA)
- Confidential information:
 - 42 pages
- Knowledge and experience gained will facilitate future H1N1 CHIM application and improve regulatory efficiency

Conclusion

- The use of reverse genetics-derived improves CHIM reproducibility and standardization
- The Dutch framework:
 - includes substantial environmental oversight
 - Regulatory timelines range from 5months up to 18 months
- Considerable international regulatory divergence remains
- Early regulator engagement is critical
- Future:
 - Greater adoption of risk-based assessment approaches
 - Exemption of RG viruses with complete wild-type sequence homology from GMO regulation
 - Increased international harmonization
 - Growing importance of gene therapies and challenge models



Thank you for your attention!



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