Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

Gene Therapy Office
-
Regulations in a rapidly emerging field

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www.loketgentherapie.nl

Presentation outline

1. Role Gene Therapy Office
2. Update GMO Office
3. Update CCMO
4. Evaluation Gene Therapy Office

1.Role Gene Therapy Office

Overview of GMO procedures in the EU

Market Authorisation — Central procedure

Regulation No 726/2004 (EMA)
Regulation No 1394/2007 (ATMP)

Clinical trials

- Medical/ethical aspects — National procedure *2001/20/EC*
  → Central procedure *(Jan 2022)*
  EU Clinical Trial Regulation (536/2014/EU)

- Environmental aspects — National procedure *2001/18/EC & 2009/41/EC*

Overview of GMO procedures in the Netherlands

Clinical Ethical

Environment

1 ccmo

Central Committee on Research Involving Human Subjects

2 Ministry of Health, Welfare and Sport → CBG MEB

Medicines Evaluation Board

3 Ministry of Infrastructure and the Environment

GMO Office

National Institute for Public Health and the Environment

Ministry of Health, Welfare and Sport

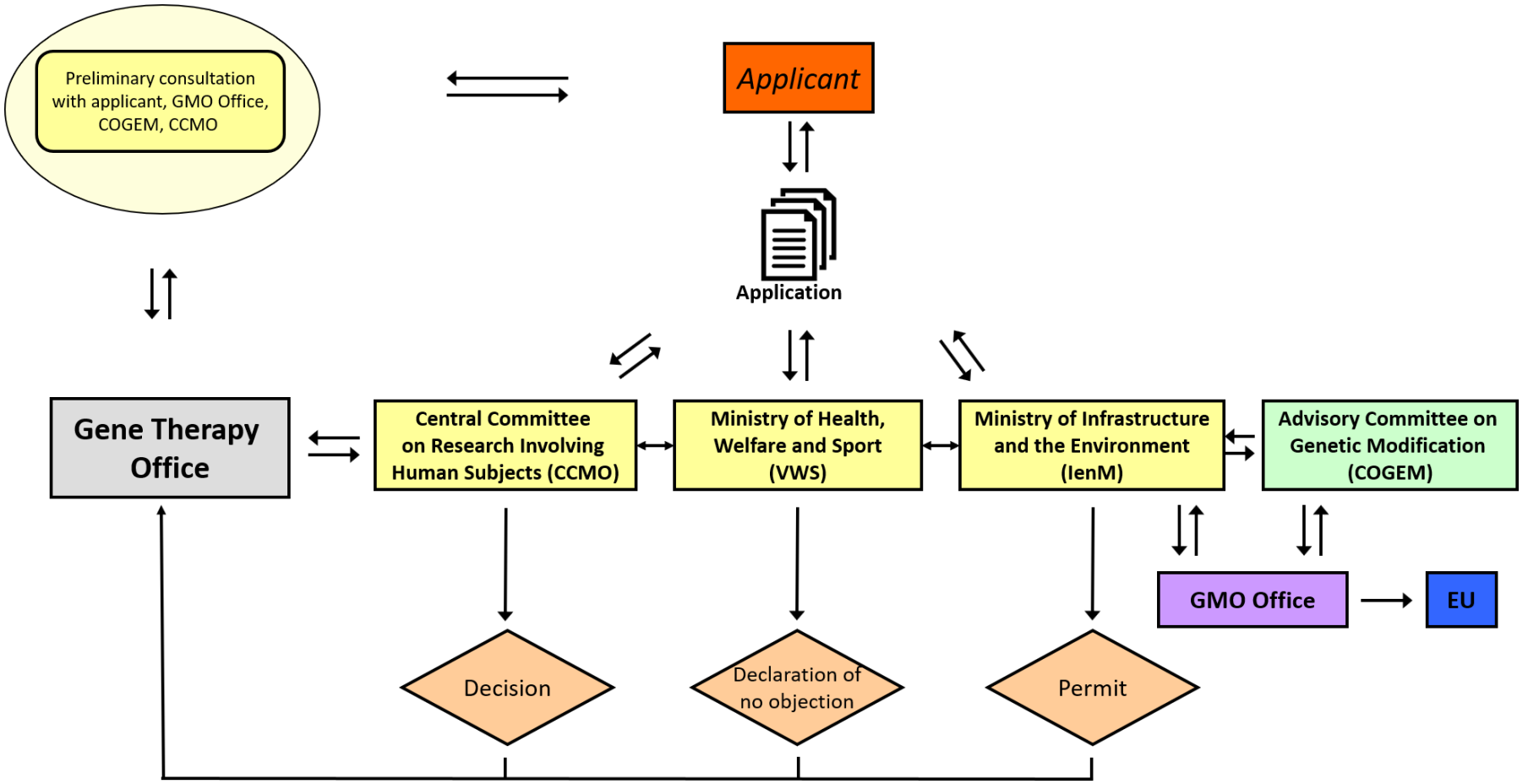
COMMISSIE COGEM GENETISCHE MODIFICATIE

Gene Therapy Office

Aim:

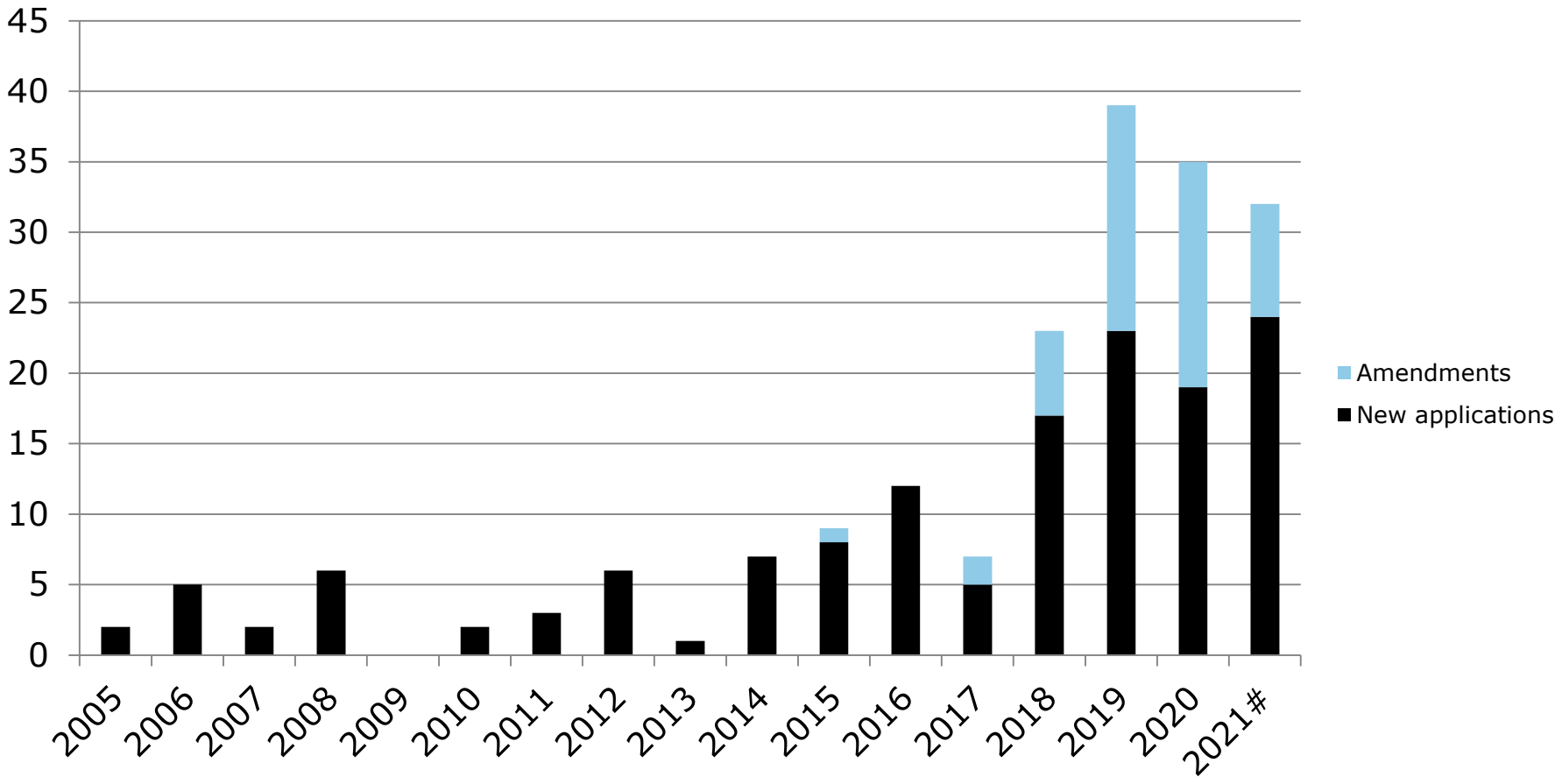
- Provide information: https://loketgentherapie.nl/
- Preliminary consultation (Vooroverleg)
- Contact point for questions
- Streamline assessment procedures

Gene Therapy Office



2. Update GMO Office

Applications for gene therapy permits at GMO Office 2005 – 2021*



*excluding retracted applications

Applications for gene therapy permits at GMO Office 2015 – 2021:

- **AAV**
- **CAR T cells/*ex vivo* transduced cells (Lenti, Retro)**
- GM bacteria
- GM parasites
- GM viruses

2015-2021: AAV + *ex vivo* transduced cells=
>70% of all applications

New options to implement streamlined GMO licensing practice

- Interplay between the GMO legislation and the legislation on medicinal products
- National simplified procedures for
  - special categories (*e.g.* AAV & gm-cells)
  - identical (copy) applications
- Permits with broad scope

Interplay between the GMO legislation and the legislation on medicinal products

-DG SANTE, EMA, EFSA, 25 Member States

- Pragmatic Approach
- Harmonization
- Within the existing legal EU frameworks

Interplay between the GMO legislation and the legislation on medicinal products

Topics include:

- streamlining environmental risk assessments
  - AAV
  - ex vivo transduced cells (LV/RV/AAV/Gene edited)
- streamlining application form(s)
  - AAV
  - ex vivo transduced cells (LV/RV/AAV/Gene edited)
  - viral vectors

Changes in national GMO regulatory framework

New situation:

- New and/or complex applications (max. 120 days)
  (existing procedure)

- Applications for permits with fixed conditions – VoV (new):
  - max. 56 days
  - ambition: max. 28 days when limited to administrative processing only

- Identical copy applications: max. 28 days (new)

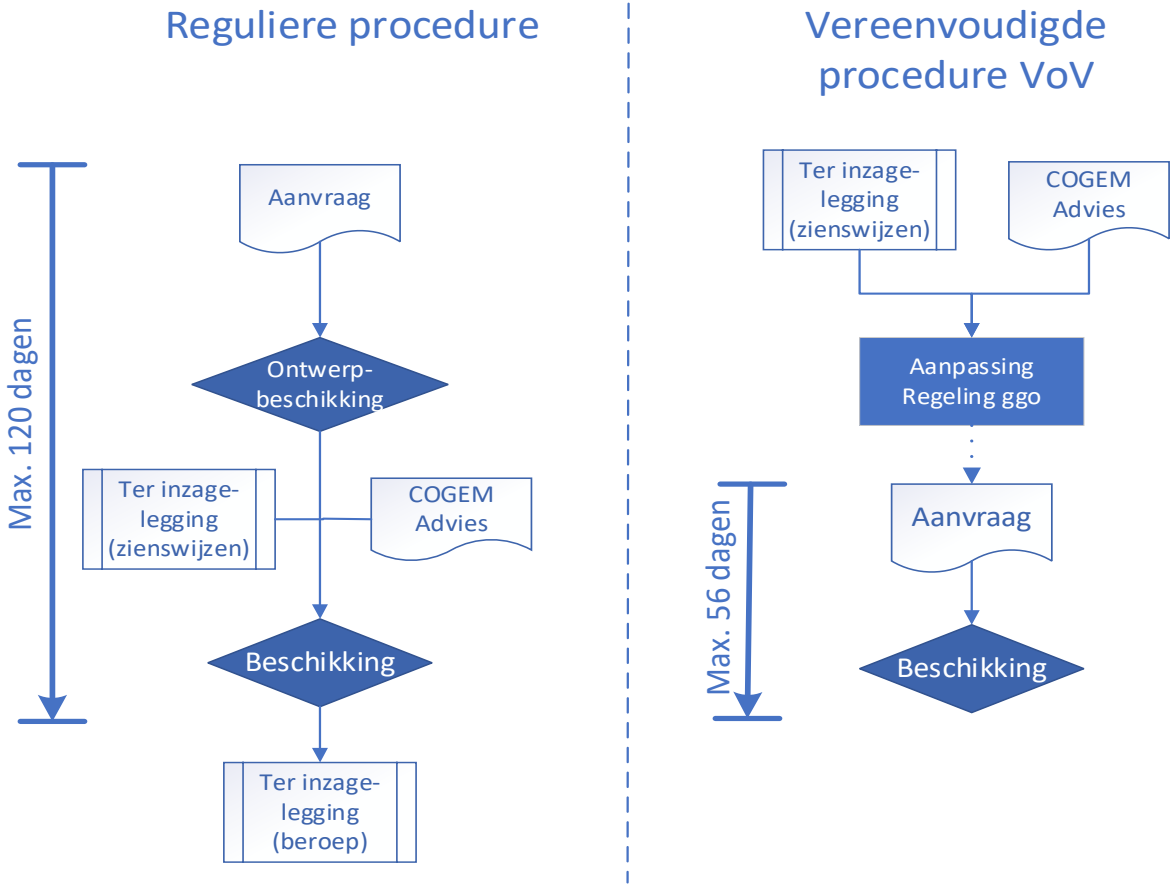
Rationale for VoV (1)

- GMO regulations are based on case-by-case assessment, unless sufficient knowledge and experience has been gained.

- When sufficient knowledge has been gained:
  - the (outcome of the) environmental risk assessment is known in advance
  - it is known within which preconditions that outcome is valid
  - it is known which regulations must (still) be imposed.

Rationale for VoV (2)

- If everything is known in advance concerning an application, standardization is possible:
  - standardized environmental RA
  - fixed application requirements
  - fixed licensing requirements
- Repeated public consultation no longer required
- So called 'learning system’: new gmo categories can be added in future



Simplified GMO procedure for AAV and ex vivo transduced cells

- Special categories (for now AAV & certain transduced cells)
- Legal procedure period max 56 days (28 days when administrative)
- 'Permits under special regulation' in Dutch Regeling ggo:
  - Art. 39: Definition of special category
    - E.g. GM AAV without harmful sequences
  - Art. 40: Information requirements
    - E.g. the purpose of the application
    - E.g. a description of the GM AAV and the modifications made therein
    - E.g. data on the absence of infectious helper virus
  - Art. 41: Binding provisions
    - E.g. Measures to prevent admixture and spread of GM AAV
    - E.g. Measures concerning storage, transport and waste processing
  - Standardized environmental risk assessment (published separately)

Fast track procedure for identical copy applications

- New fast procedure for copy requests (art. 3.10a):
  - administrative processing in a maximum of 28 days
  - no public consultation

- Conditions:
  - Only applies to identical copy requests!
  - Permit on original application formally issued
  - Limited data requirements:
    - Only enter data related to your own organization (name + address)
    - Content data of original application copy&paste in own form
    - SNIF

Broadly defined GMO applications

- GMO applications for broadly defined categories of GMOs
  - E.g. AAV clinical vectors with a non-harmful insert to treat and/or prevent disease using the generic ERA on AAV
- After permit is issued:
  - Effectively 0 waiting days for studies within scope of permit
  - Notifications in advance on specific GMO clinical study no longer required
  - Reporting on GMO activities only in legally required annual reports

3. Update CCMO

EU Clinical Trial Regulation (CTR) - 31 January 2022

- ECTR will replace the excising Clinical Trials Directive 2001/20/EC (and **not** Dir. 2001/18/EC)
- Purpose of the ECTR:
  - To simplify and accelerate clinical trials within the EU in order to make new treatment options available sooner
  - To keep the EU attractive for sponsors of clinical trials
- ECTR will harmonise the registration, assessment and supervision processes for clinical trials throughout the EU via CTIS.
  - Clinical Trials Information System (CTIS) will be the centralised (single) EU portal and database for clinical trial applications.
- Transition period of three years: During the 1st year sponsors may choose to submit a clinical trial application according to current legislation, or according to the CTR via CTIS

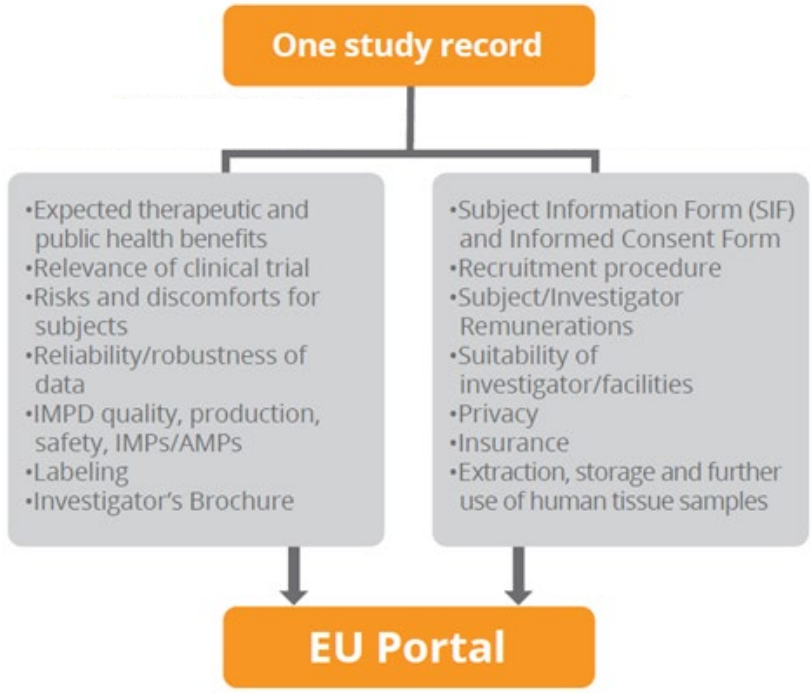
How? What's new?

- Central (single) EU portal for submissions and notifications (Clinical Trials Information System – CTIS)
- One application dossier (central part I and national part II)
- Maximum (mostly fatal) timelines for member states (MS) and sponsors
- Central coordinated assessment by reporting MS for multinational trials
- Less stringent rules for low-intervention clinical trials
- Public disclosure clinical trial information CTIS (except personal and commercial confidential information, confidential information between MSs)

EU-portal CTIS

Part I - Central

Joint assessment by concerned member states (MSC) and one reporting member state (RMS)



Part II - National

Separate assessment by each member state

Maximum timelines for member states (MS)* and sponsors

*in case of an CT with an ATMP the RMS may extend the assessment period by 50 days for the purpose of consulting with experts

Afbeelding uit DCRF brochure

More information CTR

- EMA:
  - CTIS sponsor handbook
  - Online modular training program CTIS
  - Information events on CTIS
  - Newsletter CTIS highlights with news on development CTIS
- European Commission: Q&A document with FAQ's about CTR
- CCMO: will soon publish specific information for investigators on the procedures for a clinical trial application under the CTR on CCMO website
- DCRF:
  - Brochure: The CTR in a nutshell
  - DCRF Academie: ECTR e-learing

www.ccmo.nl

Abonneer op onze nieuwsbrief!

4. Evaluation Gene Therapy Office

Update Gene Therapy Office

- Survey on Gene Therapy Office

Survey Gene Therapy Office

Goal of survey:

- Retrospective over last 5 years
- How to deal best with new developments (regulatory changes)

Main findings:

- Approachable, thoughtful, friendly and proactive
- Appreciation as information and contact point
- Organizer and access point for informal preliminary consultations

But also:

- Need for more and better pro-active communication on (regulatory) changes
- Website needs improvements