MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

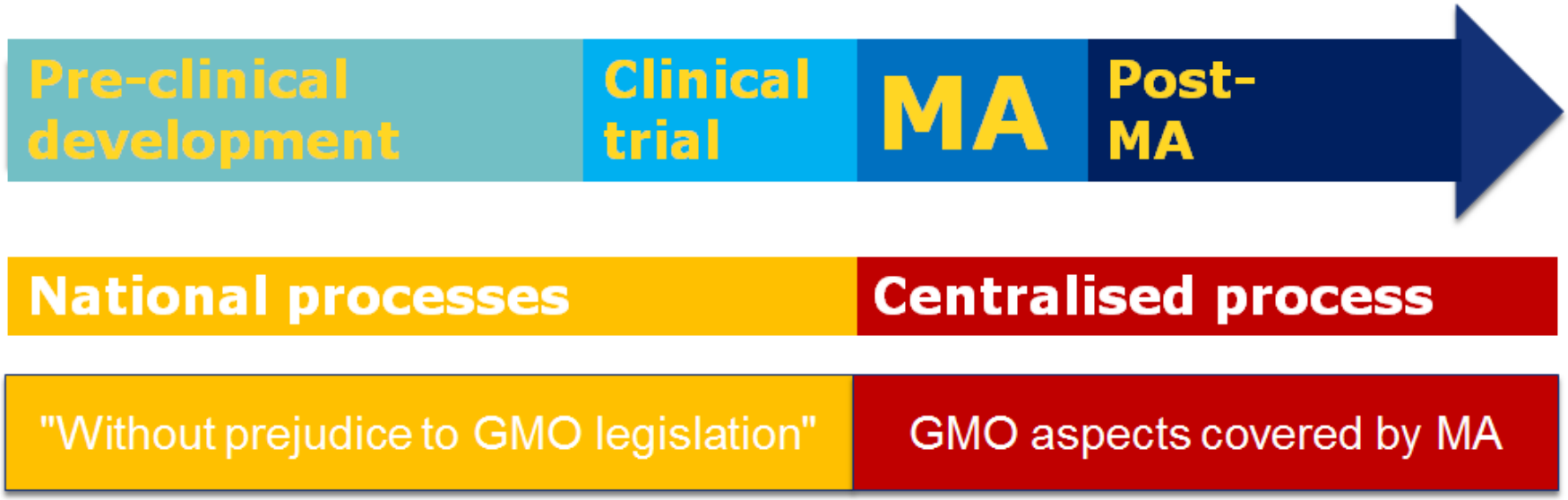
agencia española de
medicamentos y
productos sanitarios

Interrelación de la legislación de ensayos clínicos con la de organismos modificados genéticamente

Marcos Timón

AEMPS

Application of GMO framework



GMOs Medicinal Products: assessment in Europe (MAA)

GMO legislation (deliberate release) ERA GMO competent authorities normally consulted	Q, S & E assessment Pharma legislation Competent authorities (pharmaceutical)

GMOs Medicinal Products: assessment in Europe (clinical trials)

GMO assessment	Q, S & E assessment
GMO legislation	Pharmaceutical legislation
Different competent authorities	Competent authorities (pharmaceutical)

GMOs Medicinal Products: assessment in Europe (clinical trials)

GMO assessment

GMO legislation

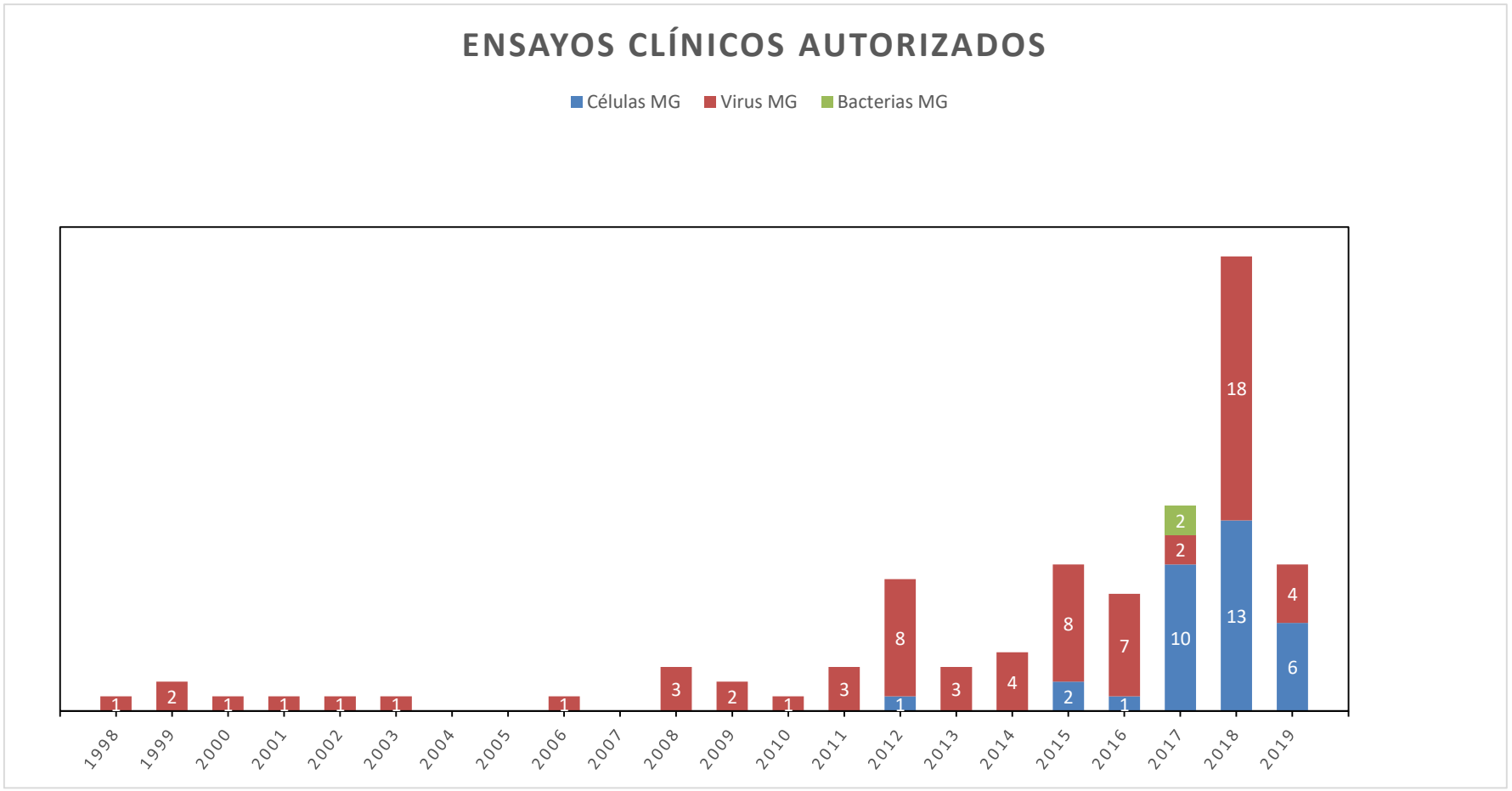
Different competent authorities

-Some MS consider deliberate release

(ERA needed)

-Other MS apply contained use

-Other MS case by case


ENSAYOS CLÍNICOS AUTORIZADOS
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EUROPEAN COMMISSION

DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

AD HOC WORKING GROUP

on the interplay between the GMO legislation and the legislation on medicinal products

THURSDAY, 9 February 2017, 10:00

DRAFT AGENDA

1. Approval of the Agenda.
2. Presentation of the main elements of the GMO legislation and the legislation on medicinal products for human and veterinary use.
3. Discussion on the interplay between the GMO legislation and the legislation on medicinal products for human and veterinary use.

   3.1. Issues of scope - Applicability of the GMO legislation to the authorisation of medicinal products for human or veterinary use.

   3.2. Procedural issues - Authorisation of investigational medicinal products and of medicinal products containing or consisting of GMOs (clinical trials and market authorisation).
4. Work methodology and next steps.
5. AOB.

27 September 2017

Possible solutions to improve the European regulatory procedures for clinical trials with Advanced Therapy Medicinal Products consisting of or containing Genetically Modified Organisms

ALLIANCE for Regenerative Medicine

ebe european biopharmaceutical enterprises

efpia European Federation of Pharmaceutical Industries and Associations

EuropaBio

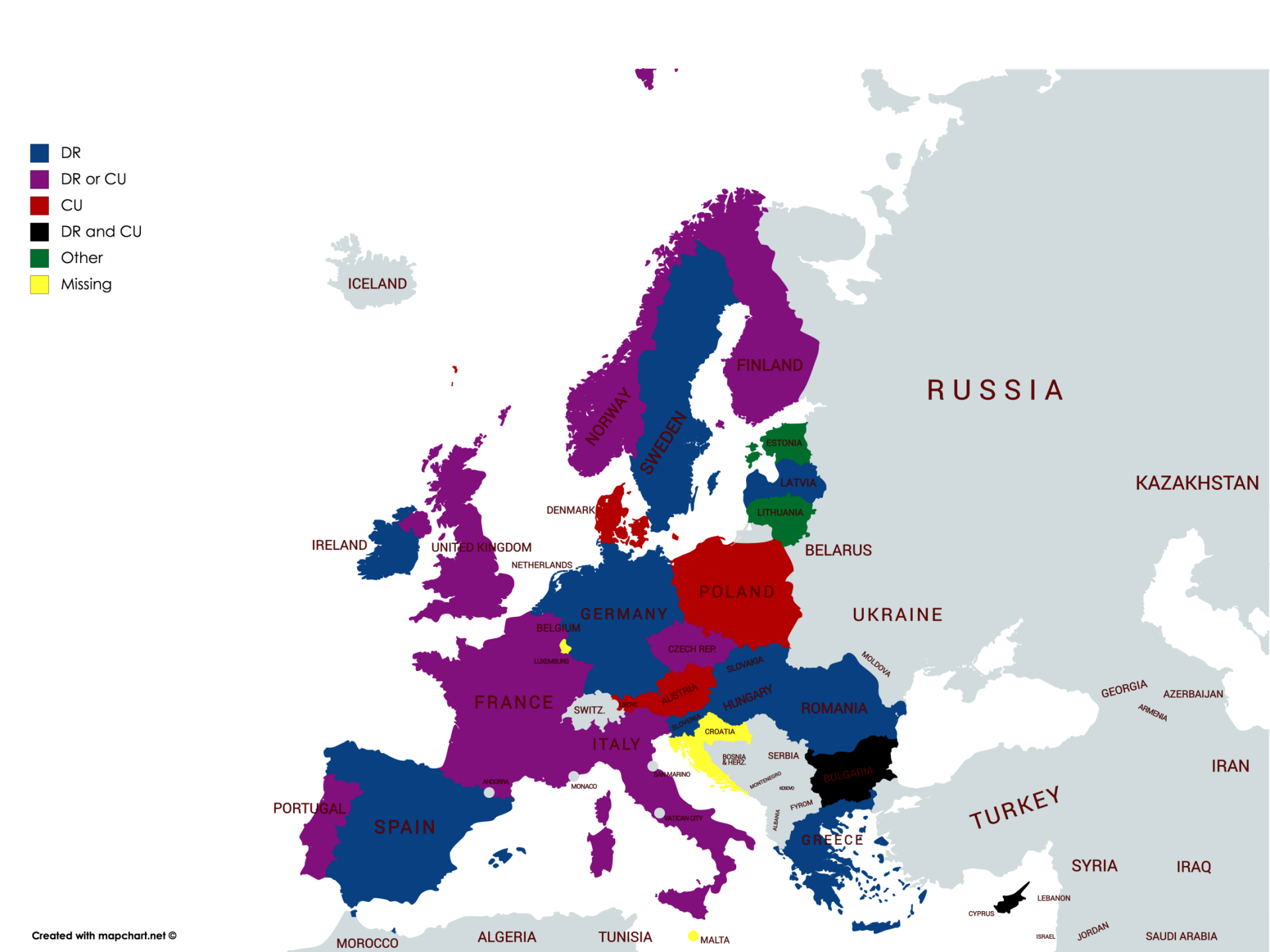
Issues identified

1) GMO legislation is not specific for medicinal products
   - -Requested information not appropriate
   - -Review of the applications not in the right context
   - -Different competent authority: possible delays, not always appropriate expertise available, etc

2) Disparity in processes and timing
   - -Applications before, in parallel or after CT approval
   - -Interactions with many other entities
   - -Repeated applications with the same ATIMP
   - -Information only in local language

3) The ERA can differ between MS
   - -Different definitions of GMOs
   - -Different legislations applied (e.g. deliberate release vs contained use)

Things will get worse with the new CT regulation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VATICAN CITY
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IRAQ
CYPRUS
LEBANON
ISRAEL
JORDAN
SAUDI ARABIA
MOROCCO
ALGERIA
TUNISIA
MALTA
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Overview of national requirements

Different approaches across EU (data from 14 MS):

- Less than 30 days: 1 MS (but publication of assessment of authorities)
- 30 days: 9 MS (in 1 MS publication includes assessment of authorities)
- 6 weeks + 6 weeks waiting period prior to implementation: 1 MS (publication includes draft decision of CA)
- 60 days: 2 MS

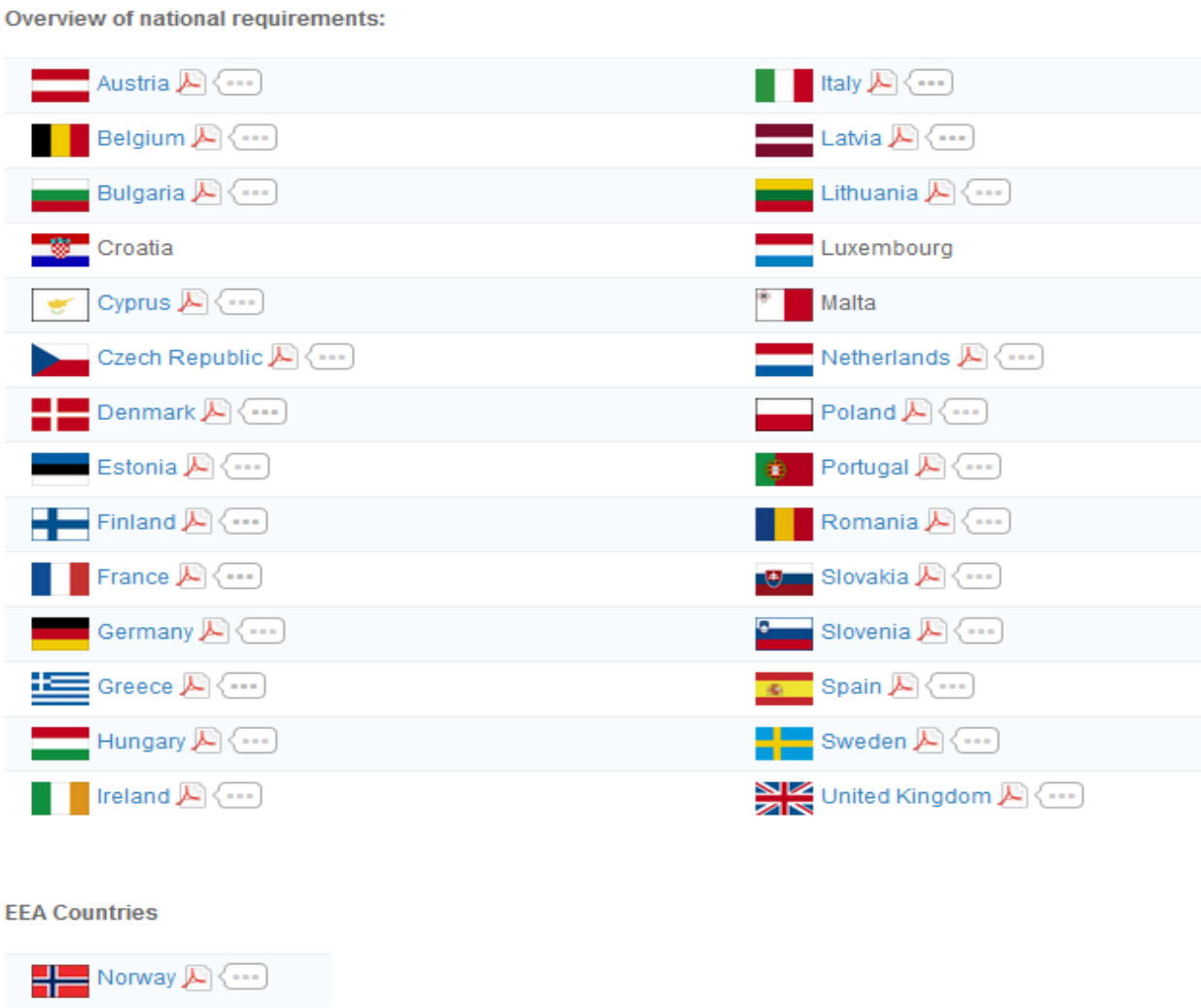
Clinical trials with gene therapy medicinal products: interplay with GMO framework

Objetivos alcanzados

Country sheets

Repository of national requirements published in:

https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_en



National procedures that must be followed for the conduct of clinical trials with medicinal products that contain or consist of GMOs

SPAIN (December 2017)

OVERVIEW OF NATIONAL REQUIREMENTS

Summary:

The GMO aspects of clinical trials with medicinal products for human use containing or consisting of GMOs are regulated under the deliberate release framework- part B of Directive 2001/18.

The applications to seek authorization under the clinical trials framework and under the GMO framework are not linked (*i.e.* the applicant can decide the timing of the submission of the GMO application).

Additional information can be found at:
https://sede.mapama.gob.es/portal/site/se/ficha-procedimiento?procedure_id=413&procedure_suborg_responsable=79&by=theme

APPLICATION FORMS TO SEEK AUTHORISATION FOR THE GMO ASPECTS

Application forms can be found at:

http://www.mapama.gob.es/es/calidad-y-evaluacion-ambiental/temas/biotecnologia/organismos-modificados-geneticamente-omg-/notificaciones-y-autorizaciones/proc_autorizacion.aspx

Language requirements:
Application should be submitted in the national language but technical documents in English are acceptable.

PUBLIC CONSULTATION

Information about public consultation on GMO aspects can be found at:
http://www.mapama.gob.es/es/calidad-y-evaluacion-ambiental/temas/biotecnologia/organismos-modificados-geneticamente-omg-/participacion-publica/liberacion-voluntaria/default.aspx

National procedures that must be followed for the conduct of clinical trials with medicinal products that contain or consist of GMOs

SPAIN (December 2017)

NATIONAL AUTHORITIES INVOLVED
Authorisation of clinical trials: • **Agencia Española de Medicamentos y Productos Sanitarios** (Spanish Agency of Medicines and Medical Devices) Contact details: Calle Campezo 1, Edificio 8, E-28022 Madrid Email: aecaem@aemps.es. Phone: +34 91 822 59 97
Authorisation of GMO aspects: • **Consejo Interministerial de OMG (CIOMG).** • **Comisión Nacional de Bioseguridad (CNB)** Contact details: Paseo Infanta Isabel, 1, 28014. Madrid. CIOMG: ciomg@mapama.es. Phone 34 91 347 65 93 CNB: secretariaomg@mapama.es. Phone 34 91 597 5650

National procedures that must be followed for the conduct of clinical trials with medicinal products that contain or consist of GMOs

BELGIUM (December 2017)

OVERVIEW OF NATIONAL REQUIREMENTS

Summary:
Depending on the characteristics and mode of administration of the medicinal product, it is possible that the GMO aspects of clinical trials with medicinal products for human use containing or consisting of GMOs do not require an authorisation under the deliberate release frameworks (Directive 2001/18/EC – Part B). When there is no possible release of the GMO in the environment that may confer a risk to human health or the environment (*e.g.* in case of GM medication taken at home, no risk of shedding, spreading,…), or if proper management procedures and/or working practices are taken to prevent any possible release conferring a risk, then a 'contained use' procedure will generally be sufficient. However, if there is a probability of possible release that may confer a risk to human health or the environment which cannot be avoided by proper management procedures or working practices, a notification under 'deliberate release' is also required.

If the framework to be followed is not clear to the applicant, it is strongly advised to request a national scientific-technical advice (STA) from the Federal Agency for Medicines and Health Products (FAMHP) prior to the submission of the clinical trial application.

Contained use (Directive 2009/41/EC)

In order to obtain authorisations under the contained use framework, a biosafety dossier should be submitted according to the Regional Decrees transposing Directive 2009/41/EC. Depending on the risk level of the contained use, a simple notification or a prior written authorization from the regional competent authority will be needed. The scientific evaluation is conducted by the SBB for all three Regions.

In case of a CTA following only the GMO contained use procedure, the SBB is the contact point for the submission of the application and to address questions related to the dossier submitted in the framework of 2009/41/EC.

Deliberate release (Directive 2001/18/EC – Part B)

The deliberate release of a GMO into the environment is regulated at the federal level.
In order to obtain an authorisation under the 'deliberate release procedure', an application is submitted to the FAMHP. The application will be evaluated by the Belgian Biosafety advisory Council which transmits its advice to the FAMHP.

An application for an authorisation under the 'deliberate release procedure' does not exempt to apply a dossier according to the Regional Decrees transposing Directive 2009/41/EC on the contained use (CU) of GMO's and/or pathogen organisms. It will need to cover all the related contained use activities (e.g. storage and handling of medication, biological samples, hospital

rooms, waste disposal).

Timeline of the submission of the applications for authorisation

The applications to seek authorization under clinical trials and under GMO frameworks can be submitted in parallel (*i.e.* the sponsor should apply for GMO authorization but does not need to wait for the GMO authorization before submitting the clinical trial application).

Additional information can be found at:
www.fagg-afmps.be/en/human_use/medicines/medicines/research_development/clinical_trials

www.fagg-afmps.be/en/human_use/medicines/medicines/scientific_technical_advice/regulation

www.biosafety.be/GT/Regulatory/Docs_guidelines/2015_07_10_Overview_Application_clin_trials%20WIV-ISP_41_SBB_15_0473.pdf

APPLICATION FORMS TO SEEK AUTHORISATION FOR THE GMO ASPECTS

Contained use:
In Flemish region: http://www.biosafety.be/CU/EN/ProceduresVGEN.html
In Walloon Region : http://www.biosafety.be/CU/EN/ProceduresRWEN.html
In Brussels Region : http://www.biosafety.be/CU/EN/ProcRBEN.html

Deliberate release:
http://www.biosafety.be/GT/Regulatory/Content_Appl_DelRel.html

Request for a national and scientific-technical advice :
https://www.fagg-afmps.be/en/human_use/medicines/medicines/scientific_technical_advice

https://www.fagg-afmps.be/en/human_use/medicines/medicines/scientific_technical_advice/applicvation_procedures

Language requirements:
The submission of the biosafety dossier of a clinical trial submitted under deliberate release may be done in English, except for the documents for the public consultation that are to be provided in the language of the region where the clinical trial will be conducted (French or Dutch).

The biosafety dossier of a clinical trial submitted under contained use comprises a technical part and a public part. Only the public part needs to be submitted in the language of the region where the clinical trial will be conducted.

National procedures that must be followed for the conduct of clinical trials with medicinal products that contain or consist of GMOs

BELGIUM (December 2017)

PUBLIC CONSULTATION

A public consultation (*i.e.* a process where information for the public is made available on a publicly consultable and dedicated website) is conducted within the context of the 'deliberate release' framework (Directive 2001/18/EC) and lasts 30 days. The public consultation starts within 5 days following the acknowledgement of receipt of the application by the FAMPH and is included in the legal timeline of 90 days that also includes a formal consultation of the Biosafety Advisory Council and the subsequent formal decision.

Under the framework of the regional decrees implementing Directive 2009/41/EC, the biosafety dossier comprises a public part, which is not made available on a public website.

NATIONAL AUTHORITIES INVOLVED

Authorization of clinical trials:

- **Federal Agency for Medicines and Health Products** (FAMHP): FAMHP (R&D) is the competent authority for approval of all clinical trials.

  FAMHP is also responsible for issuing a decision on the biosafety aspects of an application under the deliberate release framework; FAMHP takes this decision on the basis of a scientific advice of the Biosafety Advisory Council.

  Contact details: Research and development department,
  Eurostation II, 8th floor, Place Victor Horta 40 bte 40, 1060, Brussels
  Email: ct.rd@fagg-afmps.be

Authorisation of GMO aspects:

- **STA** (Scientific-Technical Advice unit) of the national Innovation Office at the FAMHP: advisory body.

  Contact details: Eurostation II, 8th floor, Place Victor Horta 40 bte 40, 1060 Brussels
  Email: sta-wta@fagg-afmps.be

Contained use:

The contained use of genetically modified organisms is regulated in Belgium at the regional level. Regional authorities from the Flemish, Walloon and Brussels-Capital Region are each

BELGIUM (December 2017)

responsible for the follow-up of administrative procedures, for authorisations and for inspections. However, the scientific evaluation is centralized and conducted by the SBB.

- **SBB:** It is involved in the scientific evaluation of clinical trials regulated under the 'contained use' framework. It is the point of contact for the submission of the application and/or queries regarding the dossier submitted under the contained use framework.
  Contact details: Scientific Institute of Public health (WIV-ISP)
  Biosafety and Biotechnology Unit (**SBB**)
  Rue Juliette Wytsmanstraat,14, 1050 Brussels
  Email: contained.use@wiv-isp.be

- **Flemish region :**
  Departement Omgeving
  Afdeling Gebiedsontwikkeling, omgevingsplanning en -projecten (GOP)
  Graaf de Ferrarisgebouw
  Koning Albert II-laan 20 bus 8
  B-1000 Brussel
  Email: omgeving@vlaanderen.be

- **Walloon region:**
  Service Public de Wallonie
  Direction Générale Opérationnelle "Agriculture, Ressources naturelles et de l'Environnement (DGARNE)
  Département des Permis et Autorisations
  Avenue Prince de Liège 15
  B-5100 Namur
  Email: DGARNE@spw.wallonie.be

- **Brussels-Capital Region**
  Brussels Institute for Management of the Environment (IBGE-BIM)
  Bruxelles Environnement-Leefmilieu Brussel
  Site de Tour & Taxis
  Avenue du Port 86C / 3000
  1000 Bruxelles
  http://www.environnement.brussels/qui-sommes-nous/nous-contacter
  Email: cjansinski@environnement.brussels; or ugeebelen@environment.brussels

Deliberate release:

- In case of a CTA GMO under the deliberate release framework, **FAMHP** is the contact point for the deliberate release procedure: ct.rd@fagg-afmps.be

- **Belgian Biosafety Advisory Council**: it is an advisory body involved in the scientific evaluation of GMO clinical trials regulated under the 'deliberate release' framework. (www.bio-council.be)

Clinical trials with gene therapy medicinal products: interplay with GMO framework

Objetivos alcanzados

Procedimiento simplificado para células modificadas genéticamente con retro o lentivirus (ej. células CAR-T) (incluyendo **formulario de solicitud común específico**)

Documento de preguntas y respuestas sobre ensayos con medicamentos OMGs ya comercializados

Células modificadas genéticamente

- Are **genetically modified cells of human origin** to be considered as GMO?
  - Human beings specifically excluded from definition of GMO.
  - Human cells not able to reproduce in environment.

Todas las autoridades rechazaron excluirlas

MINISTERIO PARA LA
TRANSICIÓN ECOLÓGICA

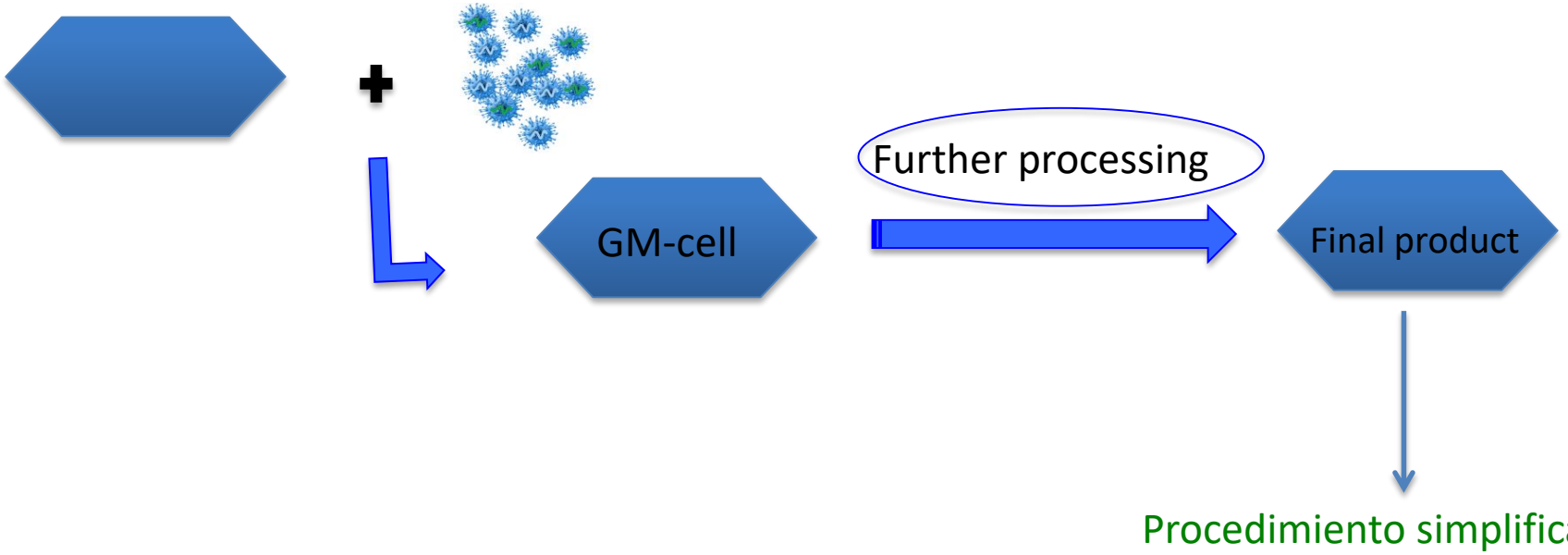
DIRECCION GENERAL DE BIODIVERSIDAD Y CALIDAD AMBIENTAL

Comisión Nacional de Bioseguridad

Buenas prácticas en la evaluación de aspectos relacionados con OMG en el contexto de ensayos clínicos con células humanas modificadas genéticamente mediante vectores retrovirales/lentivirales[1]

Si no RCV y no partículas infecciosas se puede hacer referencia a ERA estándar

Células modificadas genéticamente (mediante retro o lentivirus)



***Procedimiento simplificado:**

- ✓ Formulario común completo
- ✓ SNIF
- ✓ No se necesita hacer ERA

Anexo

ERA específico

1. Alcance

Esta evaluación específica del riesgo ambiental puede aplicarse a medicamentos en investigación que cumplan los siguientes requisitos:

(i) el medicamento en investigación consiste en células humanas modificadas genéticamente mediante vectores retrovirales/lentivirales,

(ii) el solicitante ha demostrado que no hay riesgo de formación de virus competentes para la replicación y que el producto final está libre de partículas víricas infecciosas residuales del vector que pueden liberarse en el medio ambiente de acuerdo con la Sección 3, y

(iii) el producto final está destinado a ser un medicamento sólo para humanos y se administra en centros clínicos en el contexto de un ensayo clínico autorizado.

A lo largo de este documento, el término "medicamento en investigación " se utiliza para referirse a un producto que cumple con las tres condiciones mencionadas anteriormente.

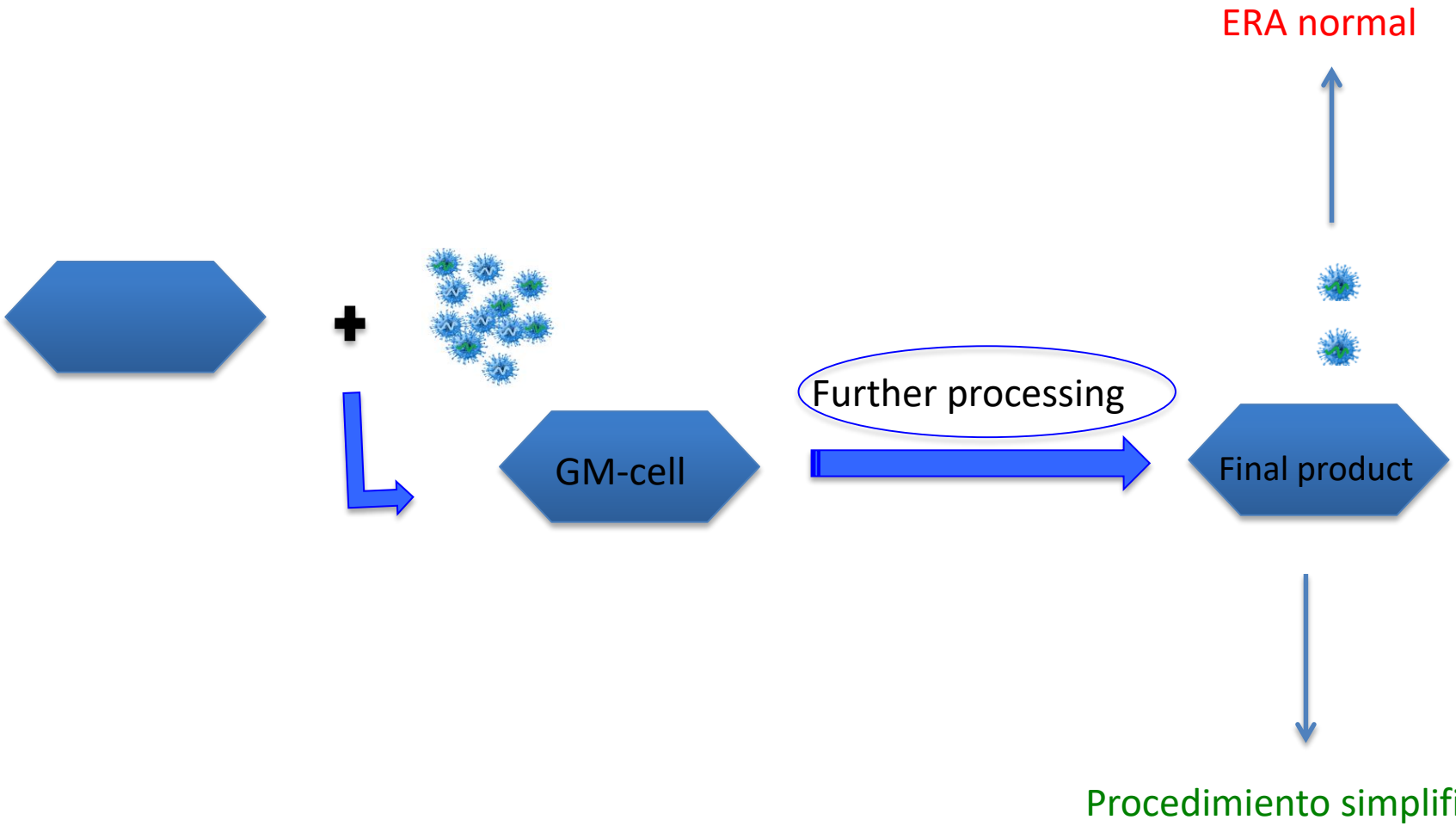
Buenas prácticas en la evaluación de aspectos relacionados con OMG en el contexto de ensayos clínicos con células humanas modificadas genéticamente mediante vectores retrovirales/lentivirales[1]

Requisitos imprescindibles:

- ✓ Demostrar ausencia de RCV y
- ✓ Demostrar ausencia de partículas víricas infecciosas

(se puede hacer mediante cálculo teórico: lavados, incubación a 37 °C, etc)

Células modificadas genéticamente (mediante retro o lentivirus)



GM-cells

- **Good Practice on the assessment of genetically modified cell by means of retro/lentiviral vectors**:
  - Streamlined approach to facilitate conduct of CTs agreed in 2018 by all MS, except BG, HR, LT, LV, NL, PL, SL, SK, and UK.
  - Key elements:
    - Common (streamlined) application form.
    - Specific ERA: negligible risks to environment.

https://ec.europa.eu/health/sites/health/files/files/advtherapies/2018_gmcells_gp_en.pdf

https://ec.europa.eu/health/sites/health/files/files/advtherapies/2018_gmcells_caf_en.pdf

MINISTERIO PARA LA
TRANSICIÓN ECOLÓGICA

DIRECCION GENERAL DE BIODIVERSIDAD Y CALIDAD AMBIENTAL

Subdirección General de Calidad del Aire y Medio Ambiente Industrial

Secretaría de la Comisión Nacional de Bioseguridad

PRODUCTOS MEDICINALES PARA USO HUMANO QUE CONTIENEN O CONSISTEN EN UN OMG: INTERRELACIÓN ENTRE LA LEGISLACIÓN DE LA UE SOBRE PRODUCTOS MEDICINALES Y OMG[1]

PREGUNTAS FRECUENTES

Versión 1

Virus Adeno Asociados (AAVs)

Documento de Buenas Prácticas

- Características de los AAV:
  - Presentes ampliamente en personas y animales
  - No patogénicos
  - Incapaces de replicar por sí mismos (necesitan un virus “helper”)
  - La mayoría del genoma propio se re-emplaza por el ADN recombinante
- Se aplicará ERA específico si:
  - Ausencia de virus competentes de replicación
  - El transgén no es peligroso

Clinical trials with gene therapy medicinal products: interplay with GMO framework

Objetivos alcanzados (Octubre 2019)

- ✓ **Procedimiento simplificado** para células modificadas genéticamente con retro o lentivirus (ej. células CAR-T) (incluyendo **formulario de solicitud común específico**)

- ✓ Documento de preguntas y respuestas sobre ensayos con medicamentos OMGs ya comercializados

- ✓ **Formulario de solicitud común específico** para **rAAVs**
- ✓ **Procedimiento simplificado** para **rAAVs**
- ✓ **Formulario de solicitud común específico** para otros **virus**

Disponibles en breve

¡Muchas gracias!