The implementation of the CTR, Clinical Trial Regulation (N° 536/2014), MDR, Medical Device Regulation (N° 2017/745) and IVDR, In Vitro Medical Device Regulation (N° 2017/746) in Belgium

and the impact on the ethical review process

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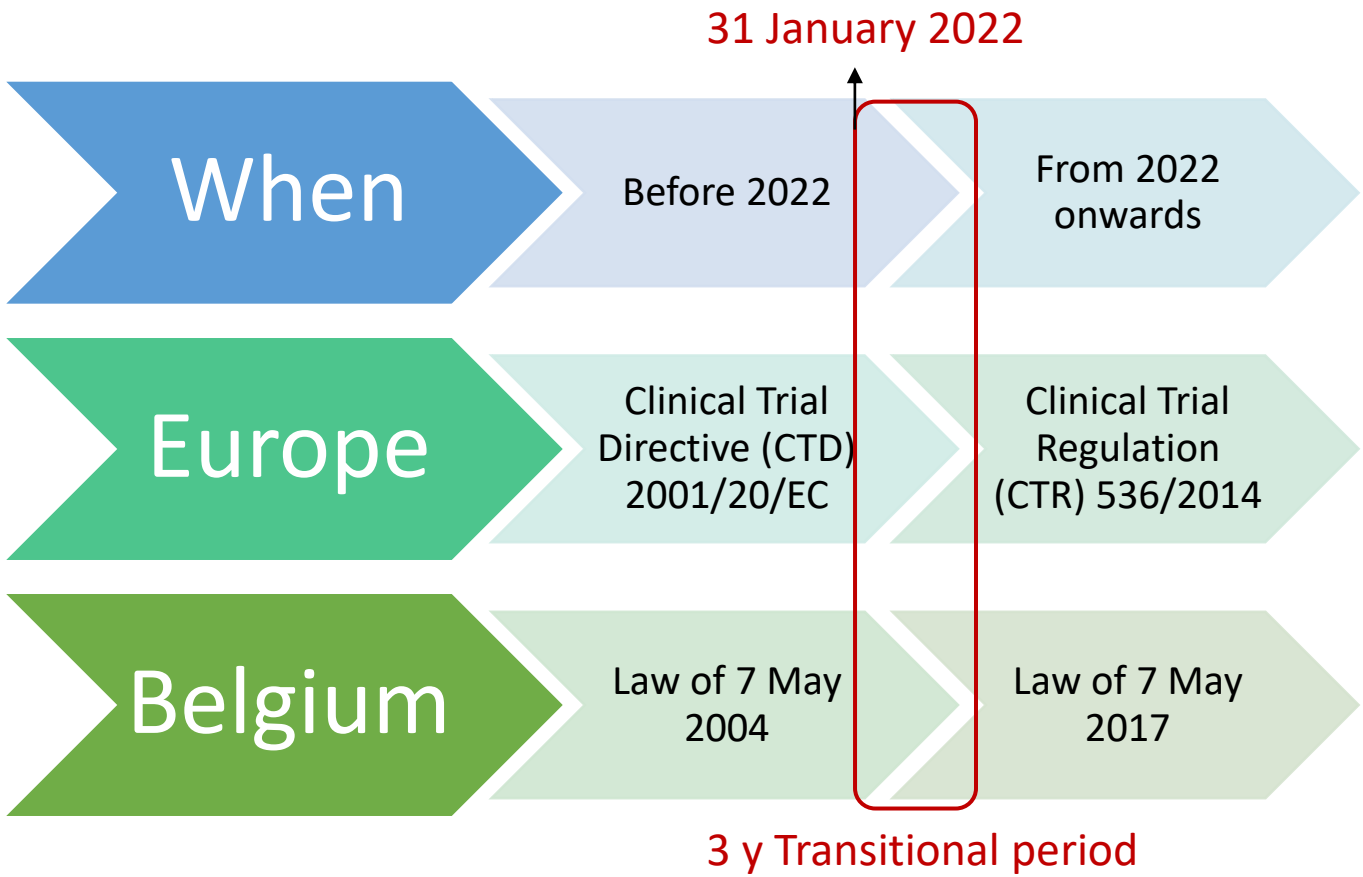
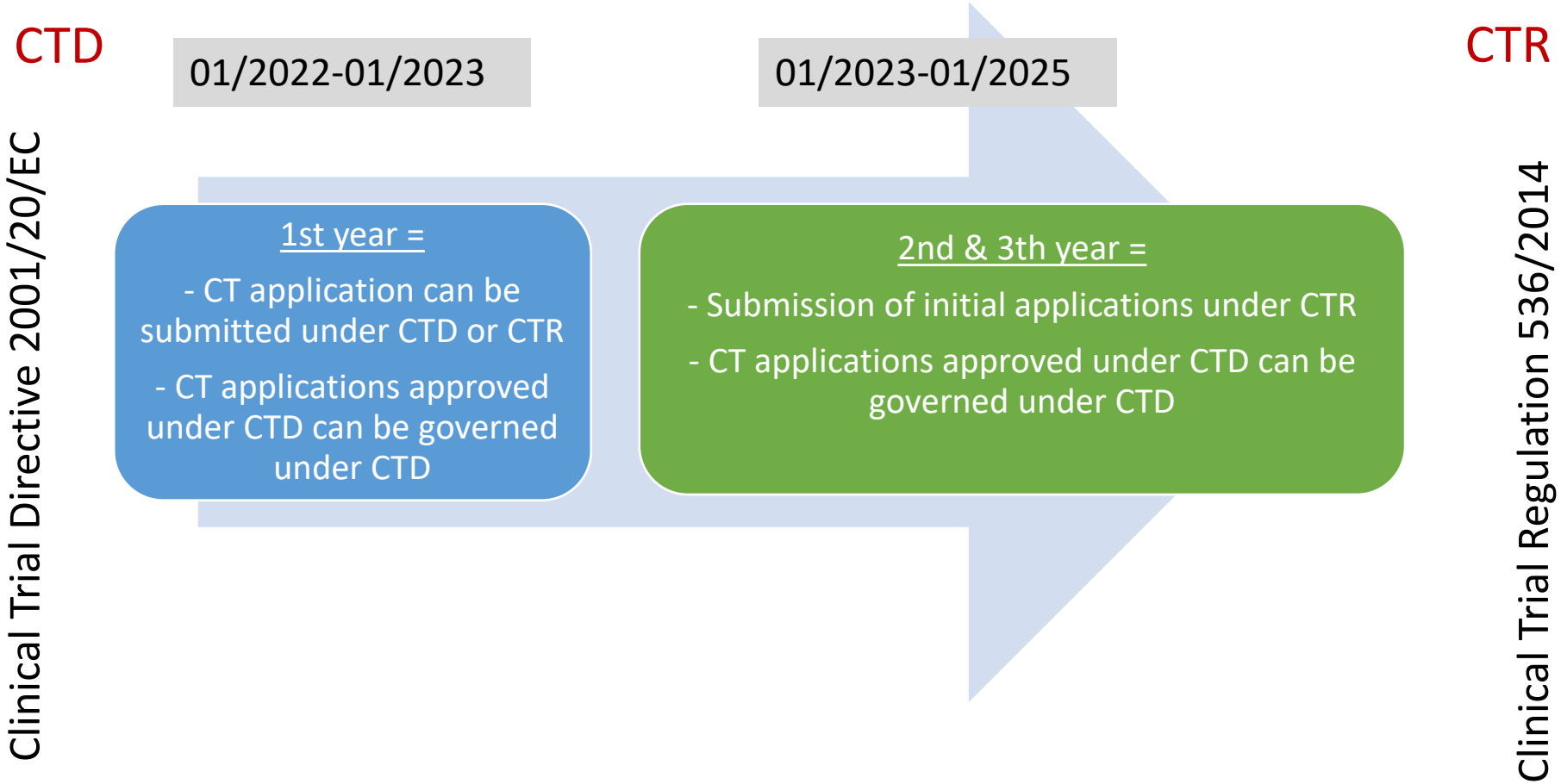
1. Clinical Trials on Medicinal Products for Human Use : Change of the Legal Context

Legal context Clinical Trials (CTs)



Transitional period (3 years)



2. Europe:

Clinical Trial Regulation (CTR) N° 536/2014
Medical Device Regulation (MDR) N° 2017/745
In Vitro Medical Device Regulation (IVDR) N° 2017/746

Objective:

To **simplify** and **harmonise** the submission and evaluation process of CT (clinical trial) & CI (clinical investigation) applications **across Europe**:

- While applying the highest standards of safety for the patient/subject and protecting their rights, dignity and well-being
- Without compromising public health

=> Create a favorable environment for conducting CTs & CIs in Europe

Highlights for Ethics Committees (ECs)

CTR

- Each MS organises itself to ensure a coordinated review of the application by the authorities and the EC and provides the single opinion of the MS within timelines of the review process

=> Need for harmonised procedures across ECs

- Persons assessing the application independent of :
  - The sponsor
  - The clinical trial location
  - The investigators involved

  and are free of any other undue influence
- Involvement of laypersons is mandatory (in particular patients or patients' organisations)
- Need for sufficiently large expertise and experience amongst the members of the EC

MDR/IVDR

- Each MS organises itself to ensure a coordinated review of the application by the authorities and the EC and provides the single opinion of the MS within timelines of the review process

⇒ Need for harmonised procedures across ECs

⇒ **coordinated assessment is not yet possible**

- Persons assessing the application independent of :
  - The sponsor
  - The investigators involved
  - natural or legal persons financing the clinical investigation

  and are free of any other undue influence
- Involvement of laypersons is mandatory (in particular patients or patients' organisations)
- Need for sufficiently large expertise and experience amongst the members of the EC

European Legislation

CTR

a) Development of a European Portal and Database

by EMA

CTIS=Clinical trial Information system

CTR is applicable only when CTIS is available (**31/01/2022**)

Coordinated review

a) 1 single application via **CTIS** for all member states (MS) concerned

b) One of these MS is designated as **reporting** MS (RMS) and provides a single opinion to the sponsor (incl coordinated review by other MS concerned)

c) within the timelines as set out in this Regulation

MDR/IVDR

a) Development of European database on medical devices Eudamed

by European Commission

MDR entered into force on **26/05/2021**, even when Eudamed is not yet available for the coordinated review

IVDR entered into force on **26/05/2022**, even when Eudamed is not yet available for the coordinated review

Coordinated review (future)

a) 1 single application via **Eudamed** for all member states (MS) concerned

b) One of these MS is designated as **coordinating** MS and provides a single opinion to the sponsor (incl coordinated review by other MS concerned)

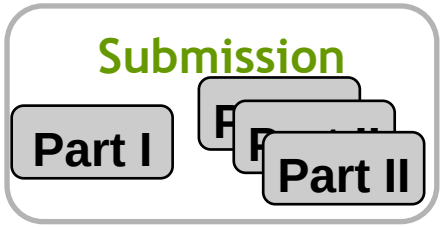
c) within the timelines as set out in this Regulation

CTR No 536/2014: some major changes

A. **Regulation** instead of **directive** (country-specific adaptations only for a few aspects)

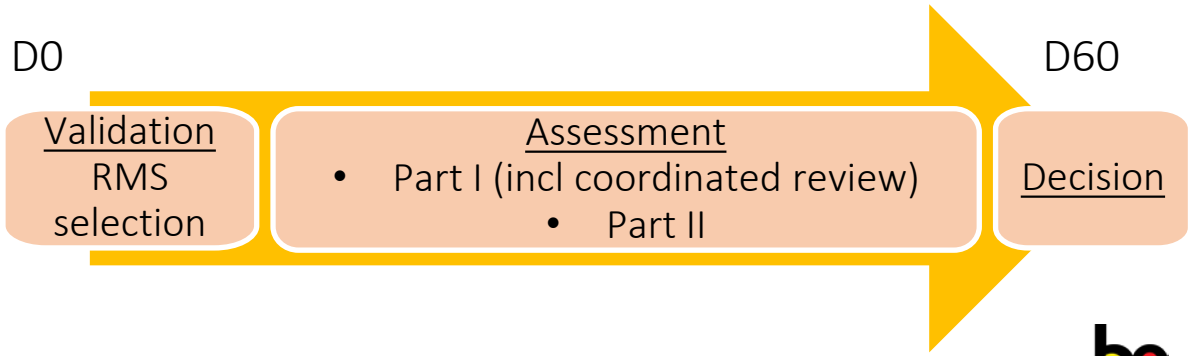
B. Development of a European Portal and Database (https://euclinicaltrials.eu/home)

C. 1 single application via the EU portal for all member states concerned (MSC)



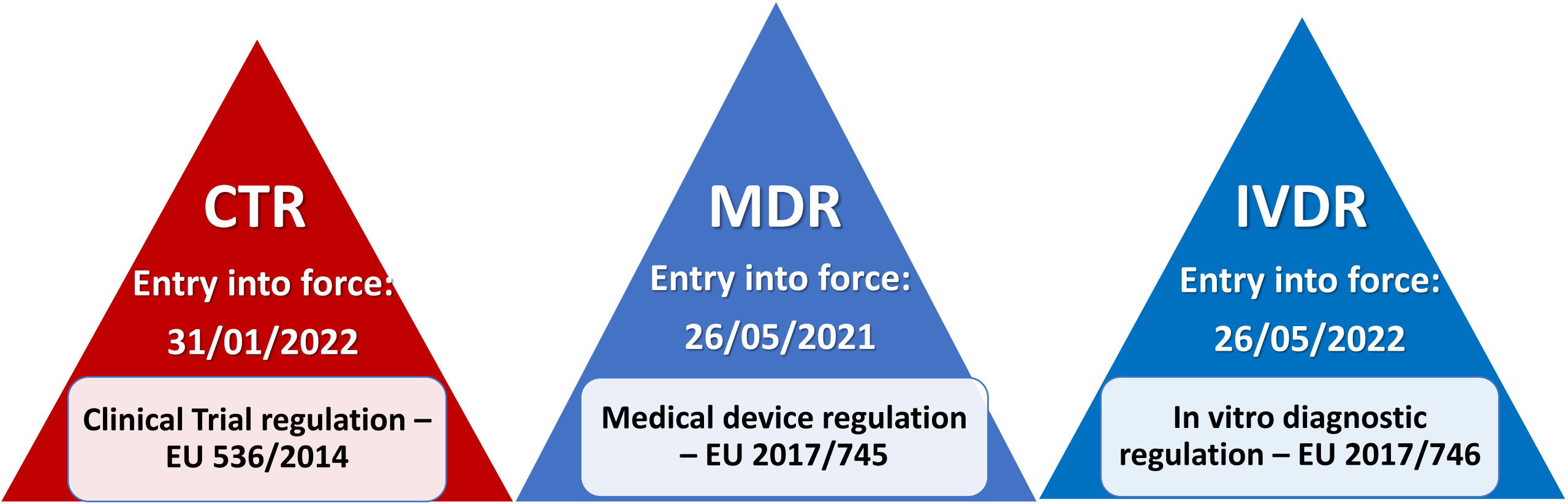
D. One of these MS is designated as Reporting MS (RMS) and provides a single opinion to the sponsor (incl coordinated review by other MSC)

E. New timelines + deadlines (tacit agreement)



3. BELGIUM:
Translation of the CTR, MDR and IVDR Requirements into the Belgian Law and the Belgian System

New European regulations

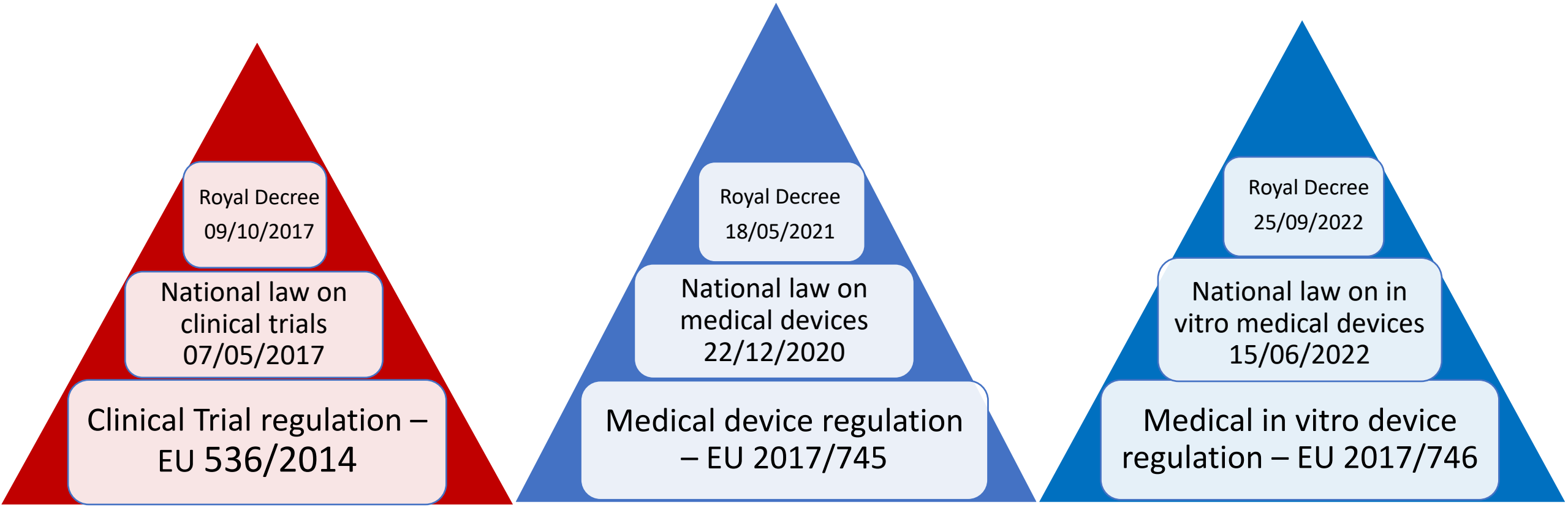


Belgian law:
7/05/2017

Belgian law:
22/12/2020

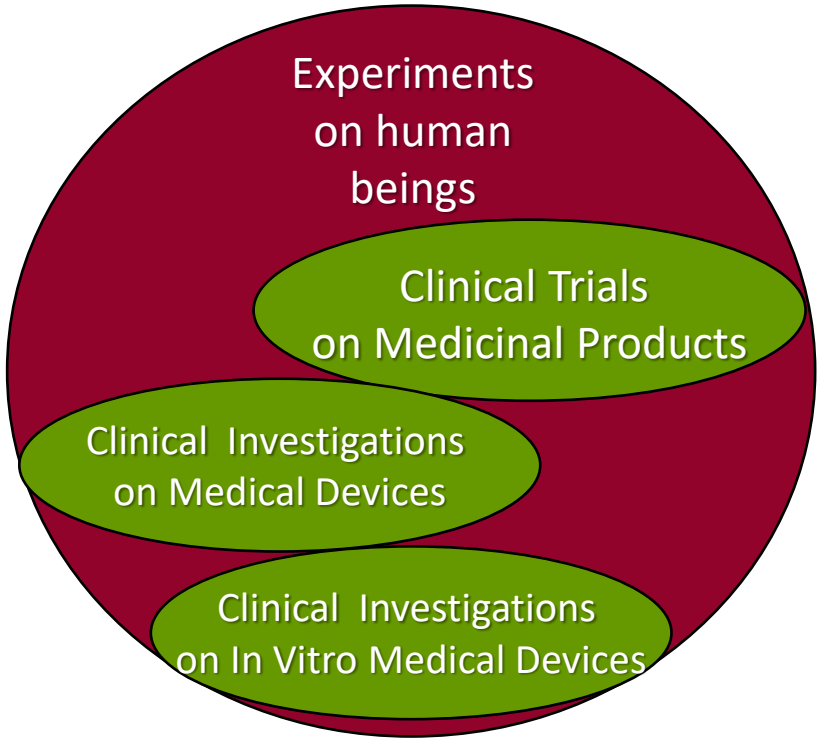
Belgian law:
15/06/2022

Belgian Legislation on CTR, MDR & IVDR



Belgian Law:

- Previous situation



Law of 7 May 2004

- Current situation

Other experiments on human beings

Law of 7 May 2004 (To be revised)

Clinical Trials on Medicinal Products

NEW Law of 7 May 2017

Clinical Investigations on Medical Devices

NEW Law of 22 December 2020

Clinical Investigations on In Vitro Medical Devices

NEW Law of 15 June 2022

Highlights of the European Regulations

CTR

CTIS=Clinical trial Information system

European portal and database developed by EMA

Coordinated review

a) 1 single application via **CTIS** for all member states (MS) concerned

b) One of these MS is designated as **reporting** MS (RMS) and provides a single opinion to the sponsor (incl coordinated review by other MS concerned)

c) within the timelines as set out in this Regulation

MDR/IVDR

EUDAMED European database on medical devices

Developed by European Commission

Eudamed is not yet available for the coordinated review

Coordinated review (future)

a) 1 single application via **Eudamed** for all member states (MS) concerned

b) One of these MS is designated as **coordinating** MS and provides a single opinion to the sponsor (incl coordinated review by other MS concerned)

c) within the timelines as set out in this Regulation

Implementation of CTR, MDR & IVDR in Belgium highlights

- National contact point (NCP): FAMHP (**Law of 7 May 2017, Art. 4; CTR, Art 83)**
- The FAMHP and the Evaluating EC are jointly in charge of the evaluation
- Reorganisation of the ethics assessment/Ecs
  - 1 independent EC involved per assessment

    Persons assessing the application independent of :
    - The sponsor
    - The clinical trial location
    - The investigators involved
    - natural or legal persons financing the clinical investigation

    and are free of any other undue influence

    Involvement of laypersons is mandatory (in particular patients or patients' organisations)

    Need for sufficiently large expertise and experience amongst the members of the EC

    Harmonised procedures amongst Ecs
- Creation of a "College"

Ethics Committee (EC) evaluating applications

Previous situation

Law of 7 May 2004

- +/- 145 active ECs
- 25 EC fully accredited (“central” ECs)
- Application dossier is submitted to
  - The competent EC of the hospital (monocentric study)
  - One competent EC and the ECs of the sites involved (multicentric study)
- Each EC has its own procedures

Procedure 2004
ECs recognized Law 2004

Current situation

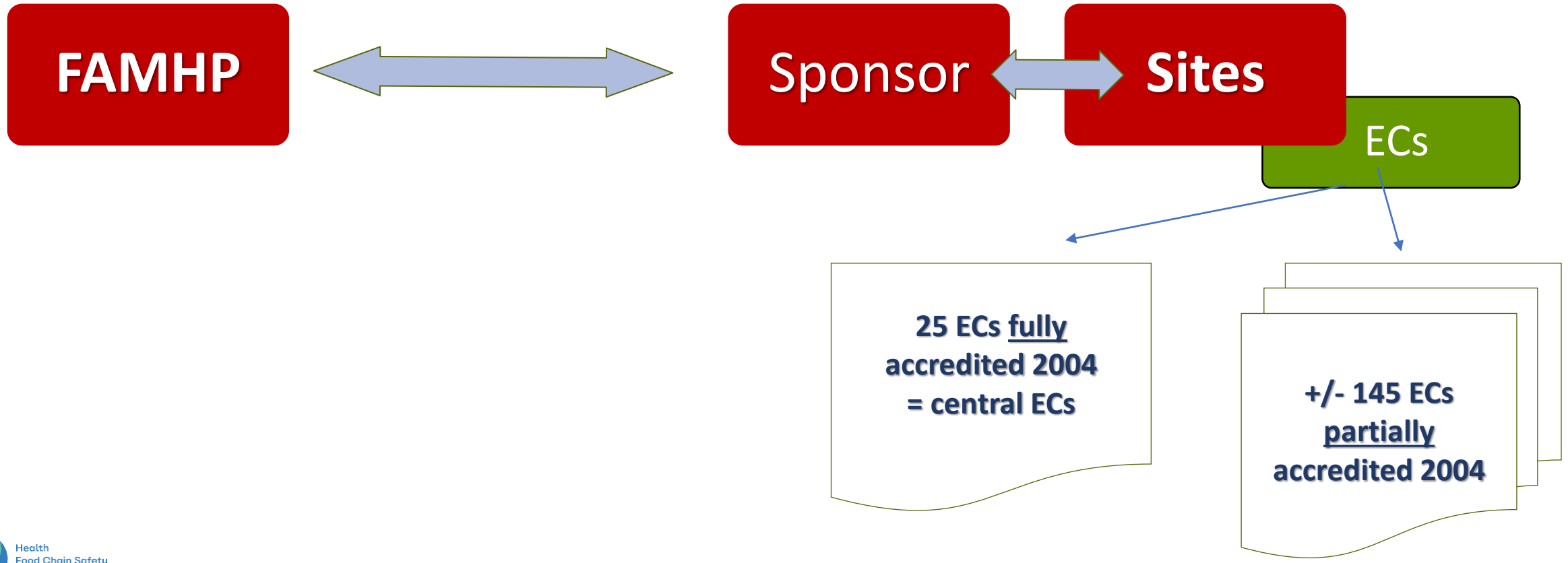
Law of 7 May 2017
Law of 22 Dec 2020
Law of 15 June 2022

- +/-15 ECs accredited + 1 independent CT College
- 1 submission of the application dossier through EU Portal
  - received by the FAMHP (national contact point)
  - dispatched to 1 EC by the CT College
  - For CTR: EU Portal CTIS
  - For MDR/IVDR: EU Portal Eudamed (not yet available)
- Harmonised procedures amongst ECs

Procedure 2017
ECs recognized Law 2017

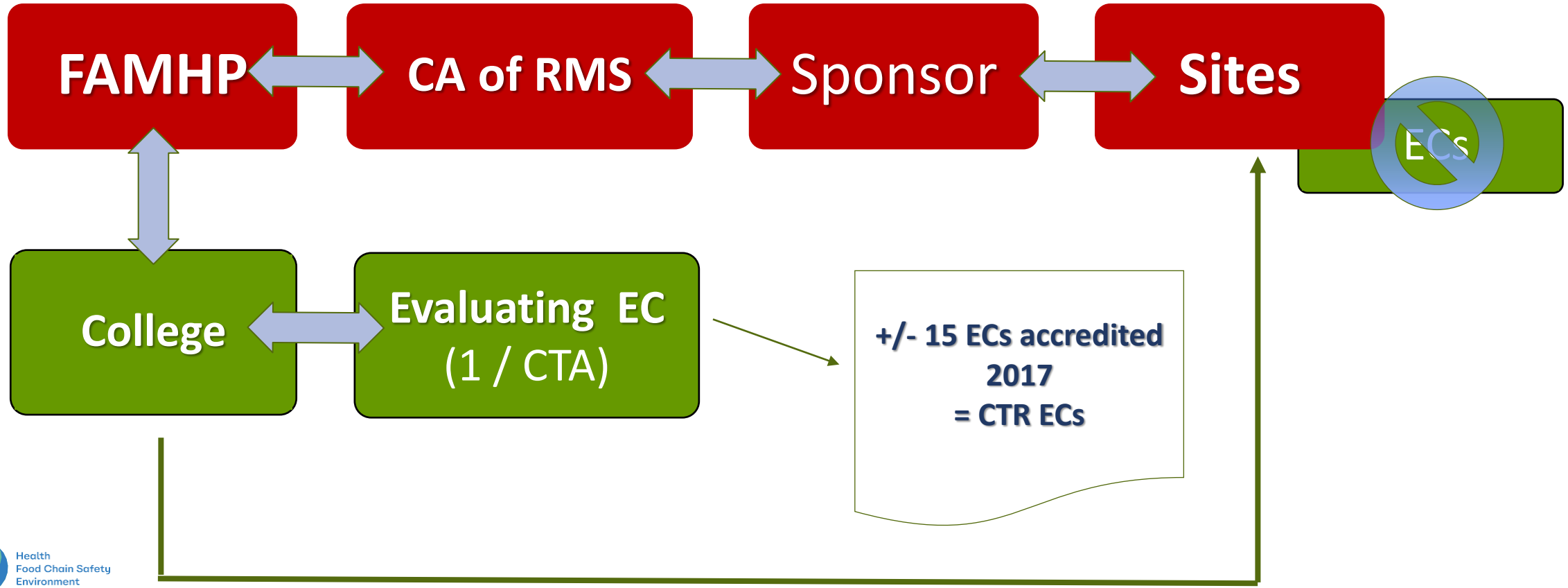
Organization of ethical review in Belgium under CTD

- **CTD & Belgian Law 2004**



Organization of ethical review in Belgium under CTR/MDR/IVDR

- **CTR & Belgian law 2017, MDR & Belgian law 2020, IVDR & Belgian law 2022**



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Creation of the College: Ministerial Decree

SERVICE PUBLIC FEDERAL SANTE PUBLIQUE,
SECURITE DE LA CHAINE ALIMENTAIRE
ET ENVIRONNEMENT

[C − 2021/41548]

18 MAI 2021. — Arrêté ministériel portant nomination des membres, du président et du vice-président du Collège visé dans la loi du 7 mai 2017 relative aux essais cliniques de médicaments à usage humain

Le Ministre de la Santé publique,

FEDERALE OVERHEIDSDIENST VOLKSGEZONDHEID,
VEILIGHEID VAN DE VOEDSELKETEN
EN LEEFMILIEU

[C − 2021/41548]

18 MEI 2021. — Ministerieel besluit houdende benoeming van de leden, van de voorzitter en ondervoorzitter van het College zoals bedoeld in de wet van 7 mei 2017 betreffende klinische proeven met geneesmiddelen voor menselijk gebruik

De Minister van Volksgezondheid,

- Independent College created within the Federal Public Service of Health, Food Chain Safety and Environment.

More information:
www.ct-college.be

- The legislation defines the mission, organisation, composition of the College and its collaboration with FAMHP and evaluating ECs.

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Composition of the College (Board)

Board	
Effective member	*Substitute member*
MDs with experience in Phase I trials	
Lucas Van Bortel, Chairman (NL)	Rene Westhovens (NL)
Didier Verhoeven (NL)	Philip Debruyne (NL)
Experts in quality control systems	
Hilde Nevens, Vice-Chairman (NL)	Joline Goossens (NL)
Lawyers	
Bruno Fonteyn (FR)	Gauthier Broze (FR)
An Vijverman (NL)	Amber Cockx (NL)

Mission of the College

1° Single point of contact between FAMHP and ECs
2° Assignment of EC in charge of evaluation of clinical study applications
- ✓ Objective criteria defined by legislation
- ✓ Cannot be the EC of the study site(s)

3° Ensure a consistent application of the law by the ECs.
Recommendations to the ECs can be made.
4° Formulate advices on the application of the regulations and legislation
5° Coordinate, harmonise, support, evaluate and follow-up the quality control activities carried out by the ECs.
Recommendations to the ECs can be made.
6° Support ECs in the evaluation of applications,
7° Submit annual activity report to Minister and Parliament

Law of 7 May 2017, Art. 9. §3

Organisation of the College
Rules of internal order: Royal Decree

SERVICE PUBLIC FEDERAL SANTE PUBLIQUE,
SECURITE DE LA CHAINE ALIMENTAIRE
ET ENVIRONNEMENT

[C − 2021/34185]

26 NOVEMBRE 2021. — Arrêté royal portant approbation du règlement d'ordre intérieur du collège tel que visé dans la loi du 7 mai 2017 relative aux essais cliniques de médicaments à usage humain

PHILIPPE, Roi des Belges,

FEDERALE OVERHEIDSDIENST VOLKSGEZONDHEID,
VEILIGHEID VAN DE VOEDSELKETEN
EN LEEFMILIEU

[C − 2021/34185]

26 NOVEMBER 2021. — Koninklijk besluit houdende goedkeuring van het huishoudelijk reglement van het College zoals bedoeld in de wet van 7 mei 2017 betreffende klinische proeven met geneesmiddelen voor menselijk gebruik

FILIP, Koning der Belgen,

Mission of the College

Tasks delegated to admin staff FPS Health

1° **Single point of contact between FAMHP and ECs**

2° **Assignment of EC in charge of evaluation of clinical study applications**

- ✓ Objective criteria defined by legislation
- ✓ Cannot be the EC of the study site(s)

3° **Ensure a consistent application of the law by the ECs.**
Not delegated: *Recommendations to the ECs can be made*

4° Not delegated: Formulate advices on the application of the regulations and legislation

5° **Coordinate, harmonise, support, evaluate and follow-up of the quality control activities carried out by the ECs**.
Not delegated: *Recommendations to the ECs can be made*

6° **Support ECs in the evaluation of applications**,

7° Prepare annual activity report for the Minister and Parliament.

Law of 7 May 2017, Art. 9. §3

Organisation of the College
Admin staff FPS Health

Administratieve Staf	
Projectleider CTR	Sébastien Vanhiesbecq (FR)
Projectleider MDR/IVDR	Michelle Fonteyne (NL)
Projectleider Kwaliteit	Katelijne Anciaux (NL)
Projectleider IT	Julien Frgacic (FR)
Dossierbeheerders	Marlène Keck-Antoine (FR) Lisa Reyckers (NL) Jean Pirard (FR) Annelies Marin (NL) Bram Ottenbourgs (NL) Julie Seronvalle (FR) Marine Gillain (FR) David Muls (NL) Myriam De Rudder (FR) Soetkin Theunynck (NL)

Organisation of the College

Admin staff FPS Health

Admin staff organizes :

- Infosessions for ECs: 4/year
- Working group meetings with ECs and FAMHP: 1/month
- Meetings College-FAMHP about dossier related issues
- CT-College Forum (Q&A sessions for ECs): 1/week
- College Board meetings: 1:month

College Board – assignment of the EC

Criteria

1) The EC must be currently **recognized** under the law of 07/05/2017
2) The EC doesn't have any quality issue
3) In case of Phase 1 CTA : the EC is **recognized for phase I** trials
4) In case of **appeal** : the EC that already assessed the dossier is excluded
5) The EC is **independent of all the sites** involved in the study and of the **sponsor**
6) The EC **expertise** domain(s) matche(s) the therapeutic domain(s) of the study
7) Language of ICFs
8) there any **connection between the study application with a former one**: e.g. in case of a
   - Resubmission
   - Extension study

MDR: definitions

See also guidance FAMHP website

- CE marking of conformity: manufacturer indicates device is in conformity with the applicable requirements set out in the MDR & other applicable union legislation

- Clinical investigation: any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance (including clinical benefits) of a medical device.

- PMCF: Post-market clinical follow-up investigation

Scope of the MDR

The “administrative pathways” are much more complex and can be schematized to ease their understanding (see diagram at next page).

The diagram shows the flows involving the College (and thus the EC recognized under the law of 07/05/2017):

1. PMCF applications with additional burdensome and/or invasive procedures,
2. CIA out of the scope of a given MD already authorized,
3. CIA with a MD not yet authorized,
4. CIA with a custom-made MD.

In this presentation, these 4 flows are summed up into 2 flows for initial MDR dossiers:

- PMCF applications (“green pathway”) and
- CIA with a consolidated opinion (“red pathways”).

Diagram of the flows described in the Belgian law of 22/12/2020

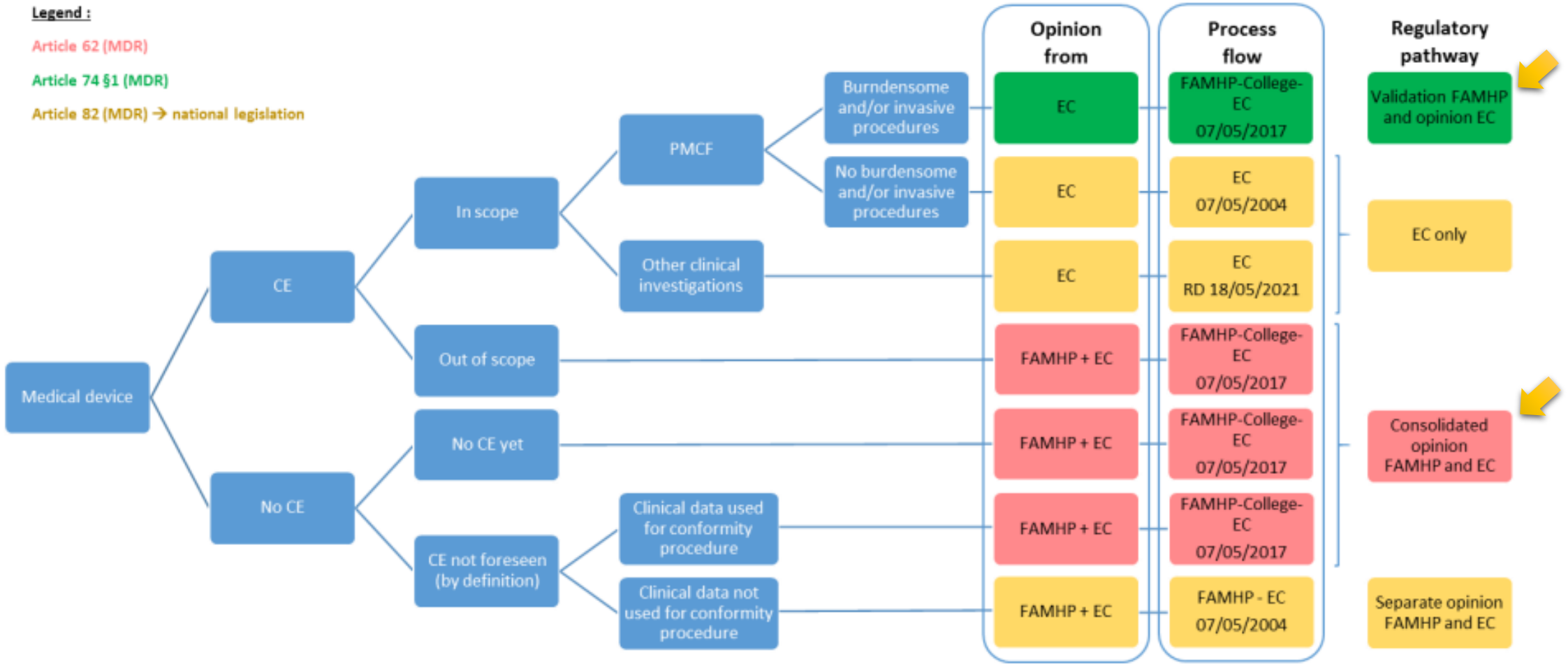


Figure 2. Different regulatory pathways. Different process flows and regulatory pathways are possible depending on the status of the investigational medical device and clinical investigation properties.

Pathways involving the CT-College and the ECs recognized under the law of 07/05/2017

PMCF applications

- PMCF applications are only within the scope of the MDR when the investigation involves additional burdensome and/or invasive procedures
  - A list detailing the classification for additional burdensome or invasive procedures for Belgium is available in the Belgian guideline document on the FAMHP website (Annex III).
- Validation by FAMHP, evaluation by the EC only
- Assessment in 22 days

Applications with a consolidated opinion

- Within scope of the MDR if
  - CIA out of the scope of a given MD already authorized
  - CIA with a MD not yet authorized
  - CIA with a custom-made MD
- Validation by FAMHP, evaluation by the EC and FAMHP
- Assessment in
  - 56 days (initial application)
  - 44 days (substantial modification)

IVDR: definitions

see also guidance FAMHP website

- CE marking of conformity: manufacturer indicates device is in conformity with the applicable requirements set out in the IVDR & other applicable union legislation

- Performance study (PS): a study undertaken to establish or confirm the analytical or clinical performance of a device

- PMPF: Post-market performance follow-up

Scope of the IVDR

The “administrative pathways” are much more complex and can be schematized to ease their understanding (see diagram at next page).

The diagram shows the flows involving the College (and thus the EC recognized under the law of 07/05/2017):

1. PMPF applications with additional burdensome and/or invasive procedures,
2. PS with surgically invasive sample-taking only for the purpose of the PS,
3. PS which are interventional clinical performance studies,
4. PS with additional invasive procedures or other risks for the subjects
5. PS involving companion diagnostics (not on left-over samples)

In this presentation, these 5 flows are summed up into 2 flows for initial IVDR dossiers:

- PMCF applications (“green pathway”) and
- CIA with a consolidated opinion (“red pathways”).
- There is also a blue pathway for PS involving companion diagnostics using left-over samples. This pathway is in scope of the IVDR but does not involve the College or the EC recognized under the law of 07/05/2017

Diagrams of the flows described in the Belgian law of 15/06/2022.

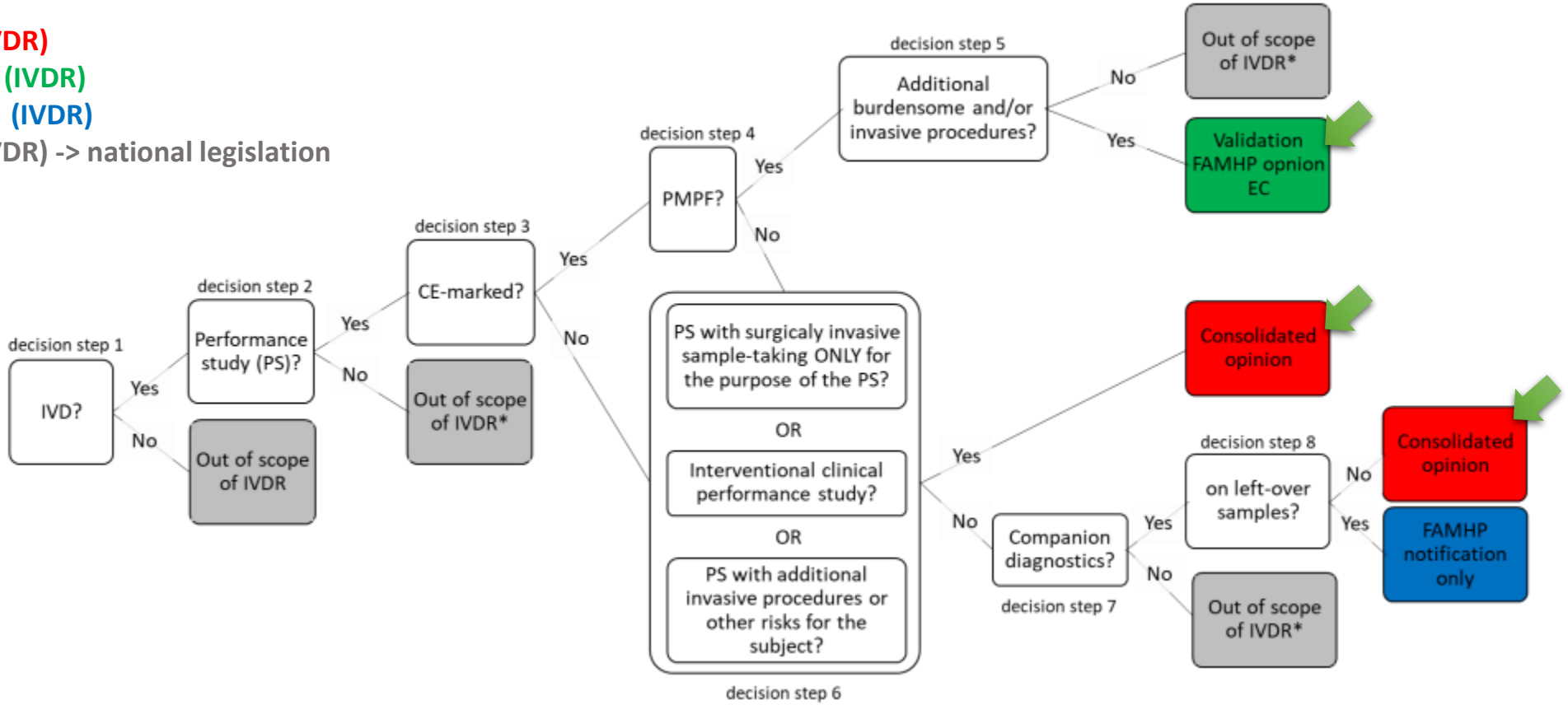
Legend:

Article 74 (IVDR)

Article 70 §1 (IVDR)

Article 58 §2 (IVDR)

Article 57 (IVDR) -> national legislation



Pathways involving the CT-College and the ECs recognized under the law of 07/05/2017

PMPF applications

- PMPF applications are only within the scope of the IVDR when the investigation involves additional burdensome and/or invasive procedures
  - A list detailing the classification for additional burdensome or invasive procedures for Belgium is available in the Belgian guideline document on the FAMHP website (Annex II).
- Validation by FAMHP, evaluation by the EC only
- Assessment in 22 days

Applications with a consolidated opinion

- Within scope of the IVDR if
  - PS with surgically invasive sample-taking only for the purpose of the PS,
  - PS which are interventional clinical performance studies,
  - PS with additional invasive procedures or other risks for the subjects
  - PS involving companion diagnostics (not on left-over samples)
    - In case of PS involving companion diagnostics only on left-over samples: in scope of IVDR but only notification to FAMHP needed
- Validation by FAMHP, evaluation by the EC and FAMHP
- Assessment in
  - 56 days (initial application)
  - 44 days (substantial modification)