Impact of the European Clinical Trial Regulation: perspective from the Belgium National Competent Authority

Immunity for health 2024

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Implementation of CTR in Belgium

Law 2017

Preparation in pilot

Collaboration within Belgium

EU working groups in which Belgium is involved

First 2.5 years of CTR in Belgium: analysis

Lessons learned after 2.5 years of CTR

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Implementation of CTR in Belgium

Law 7/5/2017

national implementing legislation in EU MS of Regulation (EU) No 536/2014

- Setting rules for the conduct of clinical trials
- Responsibilities of the competent authorities involved in clinical trials
- General provisions on the protection of trial participants
- Description of the authorization procedure of a clinical trial and substantial modifications

Implementation of CTR in Belgium

Preparation

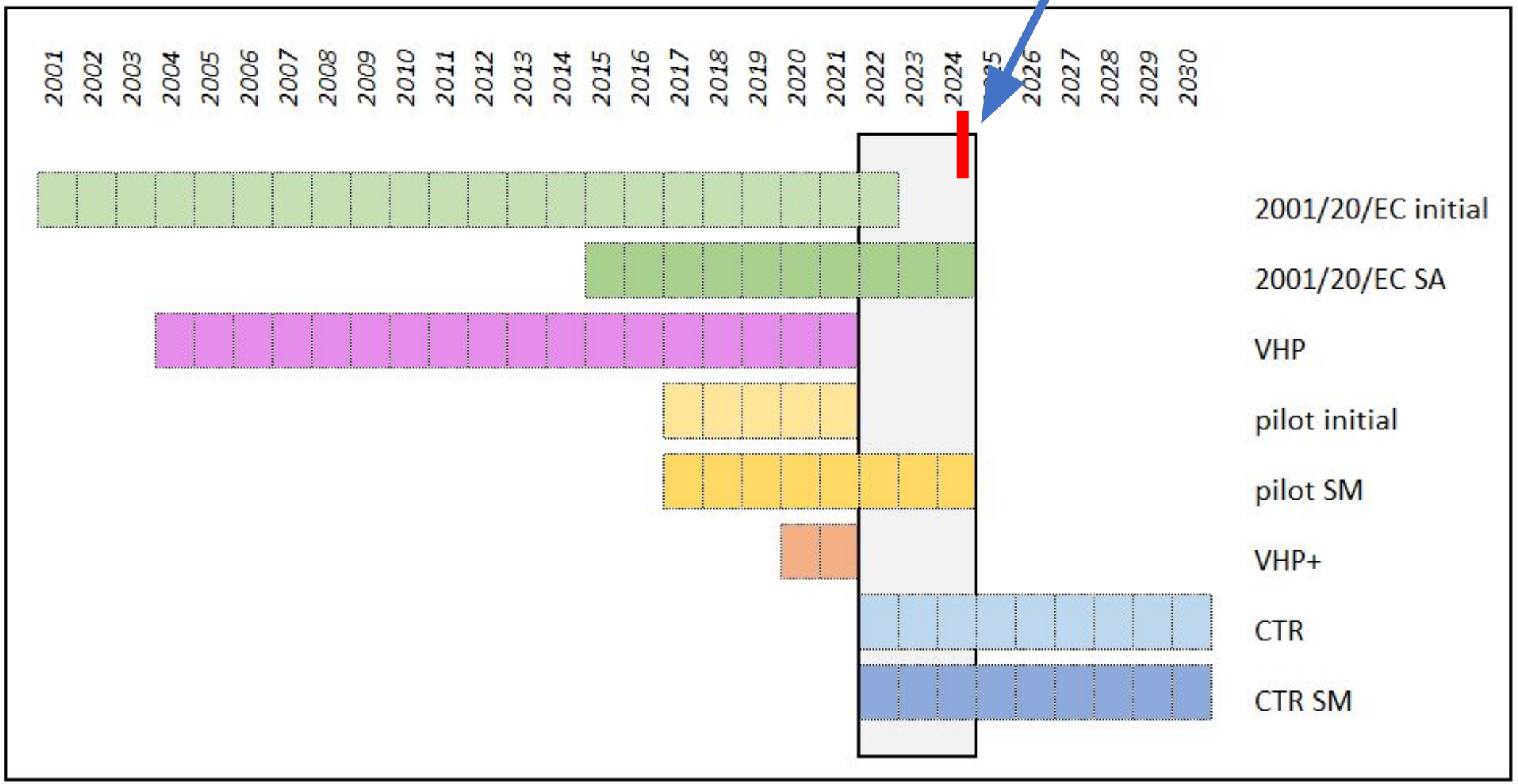
- pilot project in Belgium to prepare for CTR
  - 500 initial submissions and 2000 substantial modifications between May 2017 and November 2021
  - In collaboration with 15 ethics committees / College
  - Evaluation template according to CTR
  - FAMHP: single point of contact for submission, consolidation of evaluation and interaction with sponsor
  - Two decisions sent to sponsor by e-mail

- Belgium participated in VHP and VHP+ procedures launched at EU level to prepare for CTR
  1. Request for VHP
  2. Coördinated assessment (VHP+: participation of the evaluating EC in the assessment)
  3. National phase

Implementation of CTR in Belgium

Preparation

Transition periods:
31/1/2022
31/1/2023
31/1/2025



Collaboration within Belgium: NCA and ECs

Validation Part I	Validation Part II
FAMHP	FAMHP
Evaluation Part I • Assessed centrally by RMS • Coordinated review based on assessment report of RMS *anticipated benefits, risk and inconveniences, IMPs & AMPs, labelling, IB*	**Evaluation Part II** • National review • In parallel with Part I or separately but within 2 years *ICF, patient compensation, suitability of investigators and sites, privacy, insurance, biological samples*
FAMHP + participation EC (College)	EC (College)
Conclusion Part I	Conclusion Part II
Decision	

EU working groups and projects where Belgium is involved

CTCG: clinical trials coordination and facilitation group

HMA working group of experts from National Agencies, collaboration with EMA and EU Commission

Mission is to increase the attractiveness of the EU/EEA for clinical trials

- Harmonisation and optimisation of the regulatory environment
- Assuring protection of rights, safety and wellbeing of the subject
- Assuring the generation of robust data
- Monitor trends and evolutions in innovative trials: guidance document

CTCG Best Practice Subgroup

Produce both internal and external best practices based on experiences

CTR Collaborate project

Promote health, ensure safety, harmonise procedures; foster interaction between NCAs and Ethics in EU/EEA

EU working groups and projects where Belgium is involved

CTAG: clinical trials coordination and advisory group

EC working group of NCP from National Agencies, established in CTR:

Mission is to assist the Commission in coordinating the collaboration between member states

- Support exchange of information on the experience on CTR
- Prepare recommendations on criteria regarding the selection of reporting member states

EU4Health CT Cure

Provided harmonized and accelerated assessment of multinational clinical trial applications submitted in CTR (via CTIS) for COVID-19 therapeutics

ACT EU PA7: consolidated advice on clinical trials

Scientific advice coordination between clinical trial approval and clinical trial design in the European medicines regulatory network: SNSA, pre-CTA

ACT EU PA11: clinical trials in PHE

Activities that aim to facilitate large and multinational clinical trials in the European Union (EU) to promptly tackle public health emergencies.

EU working groups and projects where Belgium is involved

MedEthicsEU:

Group of national representatives of medical research ethics committees (MRECs)

Mission is to strengthen collaboration between the MRECs across Member States (CTR, MDR, IVDR)

- discussion between MRECs on differences related to structures, work procedures and positions
- align and promote harmonisation on operational procedures of MRECs in compliance with ethics standards
- establish cooperation related to research ethics matters with relevant European level entities (CTAG, EMA, CIE, IVD subgrop MDCG)
- Cooperation with CTCG

Combine project

Regulation (EU) 536/2014 on clinical trials of medicinal products for human use (CTR), Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR)

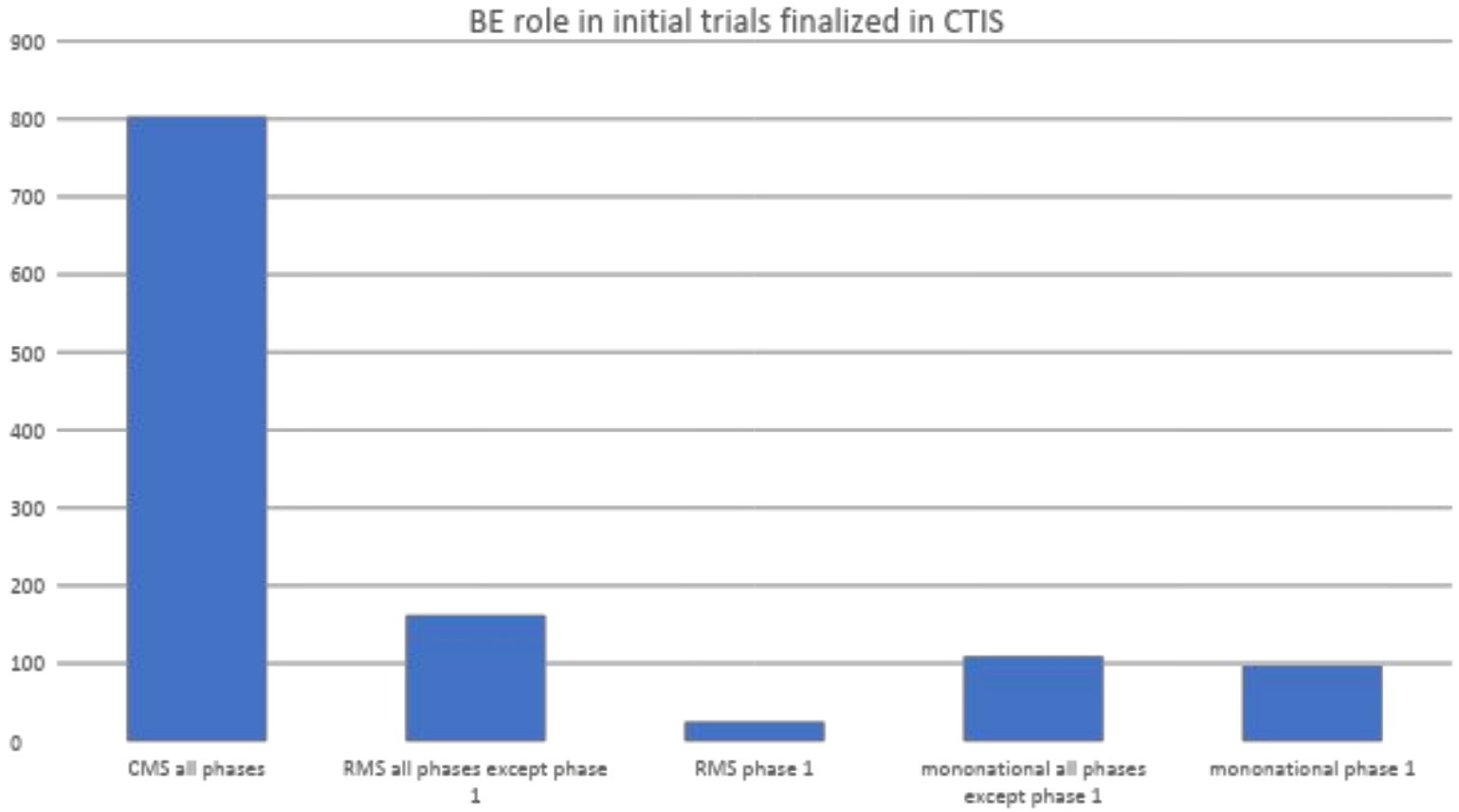
Numbers after 2,5 years of CTR in Belgium (until 30/6/2024)

- 1196 initial dossiers finalized in CTIS for which Belgium is involved:
  - 206 mononational dossiers, of which 97 phase 1 trials
  - 990 multinational dossiers with BE as MSc, of which 187 RMS ships
  - 596 transition trials and 600 ‘new’ initial trials

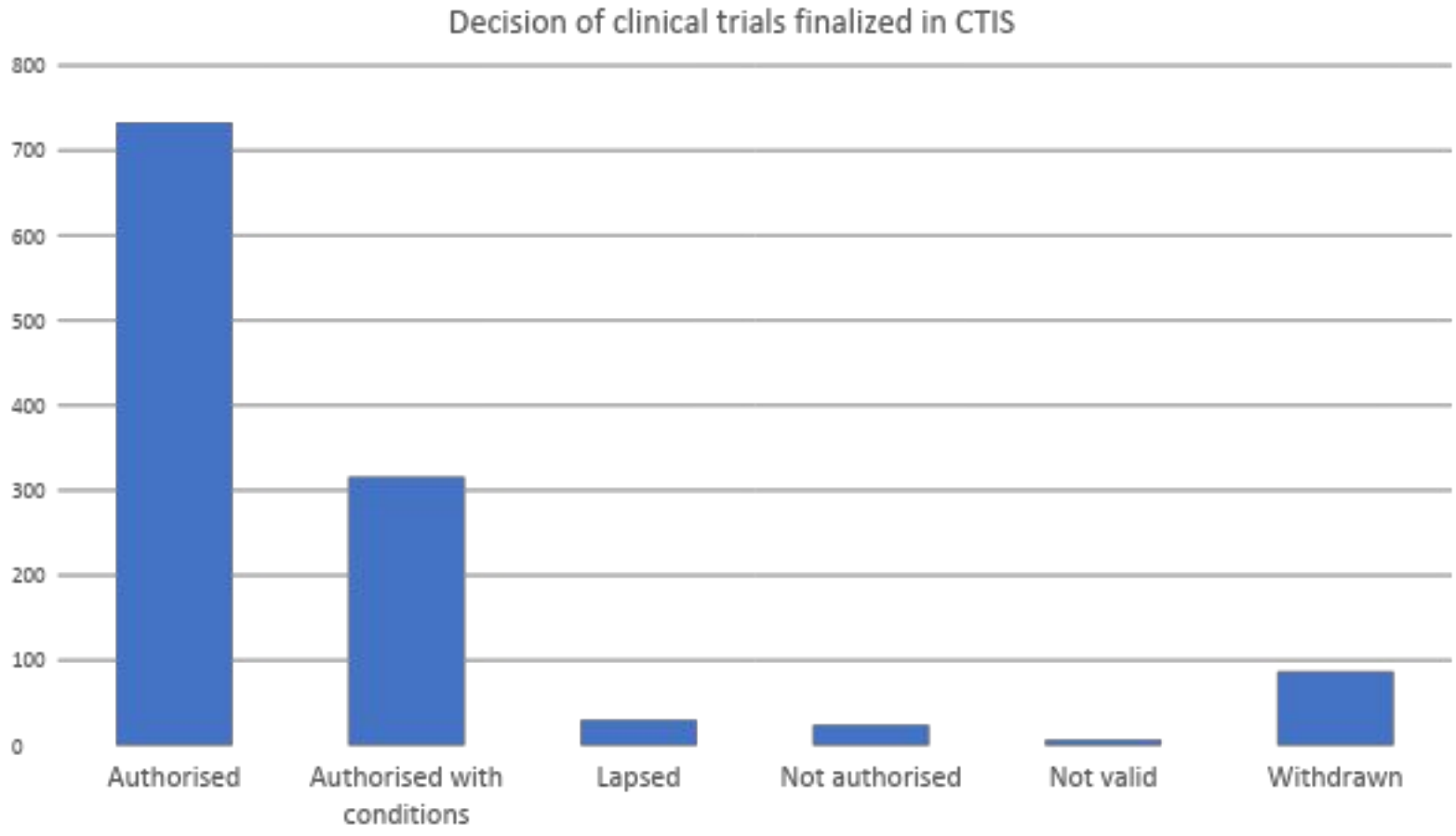
To be interpreted with caution:

- first transition phase was voluntary, only few dossiers
- ‘finalized in CTIS’ □ 3 months lost in remaining 1year and 5 months
- second transition phase (with numbers of 1 year 2 months) impacted by the many transitions to be made

Numbers after 2.5 years of CTR in Belgium (until 30/6/2024)



Numbers after 2,5 years of CTR in Belgium (until 30/6/2024)



Vaccine trials 2022 – 2023 in CTR (until 31/12/2023)

81 initial vaccine trials in EU

- 11 transition trials and 70 ‘new’ initial trials
- BE in MSc in 19 trials:
  - 9 mononational trials
  - 10 multinational trials, of which 6 trials with Belgium as RMS
  - 4 transition trials and 15 ‘new’ initial trials

Lessons learned and feedback after >2.5 years of CTR

- Predictability of evaluation will lead to a more efficient process: we shared focus points from clinical and non-clinical evaluations with stakeholders (FIH guideline interpretation, etc.)

- Lengthy lists of RFIs are considered a burden:
  - Collaborate project: worksharing and peer-review of reports of member states, however RMS in charge of consolidation
  - Continuous discussions with College/BAREC/EC

- Conditional approvals lack clarity: conditions only for critical issues, it should be clear whether it prevails the study to start (exceptionally), analysis to improve consistency

Lessons learned and feedback after >2.5 years of CTR

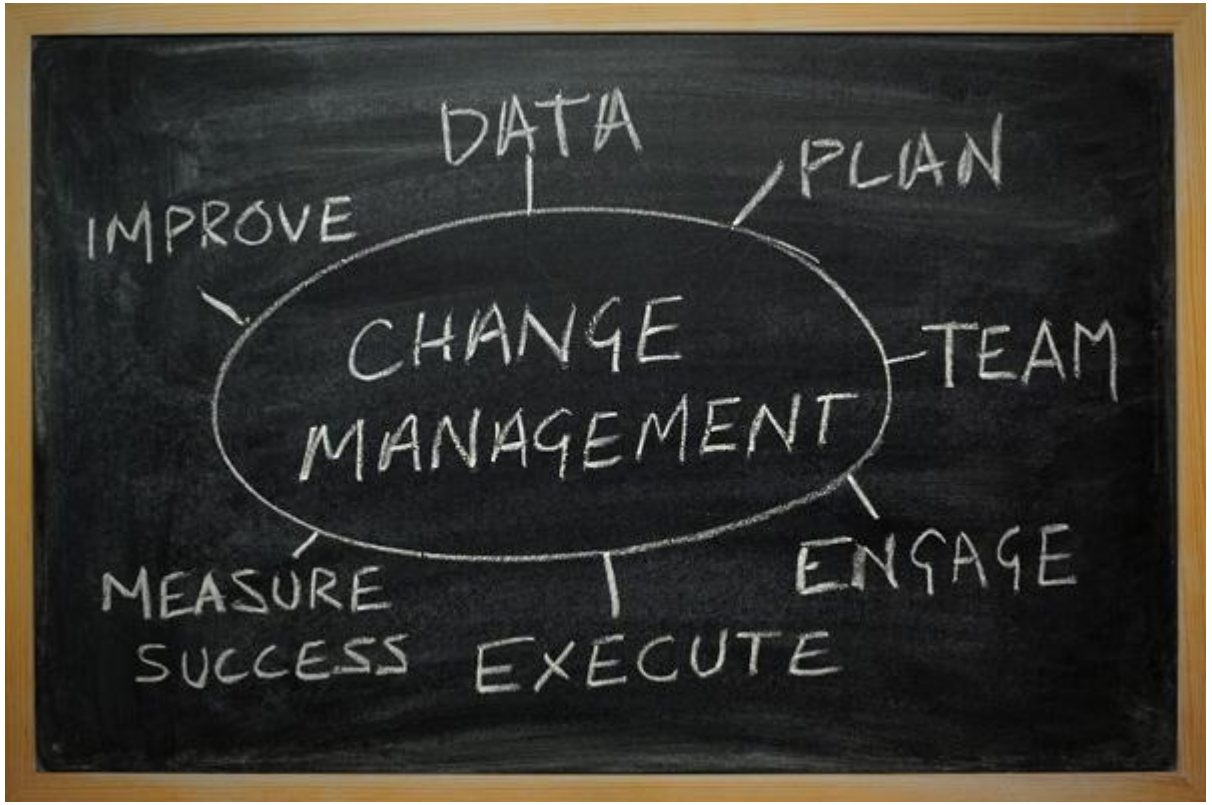
- « Combination » trials need coördination:
  - With BAC for GMO's and biosafety legislation – simultaneous assessment process ongoing
  - With FANC for radiopharmaceuticals – simultaneous assessment process in pilot
  - With MDR and IVDR - simultaneous assessment process pilot starting soon
- CTIS is a minimum viable product with:
  - (decreasingly) number of bugs
  - limited functionalities (e.g. article 11 staggered submission, notification as e-mails..)
- CCI issues posing risk for disclosure and requiring a lot of redaction: adaptations to transparancy rules

Lessons learned and feedback after >2.5 years of CTR

- CTR results in longer timelines compared to Directive trials before:
  - Expedition of mononational phase 1 trials (66 days max, but mean of 43 days so far)
  - Seasonal vaccines: solution sought for all MS in interest of public health
  - Initiatives for expediting (CT Cure, PA 11, seasonal vaccines, multinational accelerations)
- Coördination between sponsors an sites became more difficult: responsability of sponsor to share essential documents, ICH E6 guideline to GCP
- Belgium needs to be more visible on its achievements:
  - clinical dashboard is in draft
  - ATMP as innovative spearhead domain
- Follow-up the trend (a possible decline?) in Europe based on numbers provided by EMA with coöperation of member states

Reminder: please transition your trial!!!

Webinar on transition of trials from CTD to CTR (PDF - Video)



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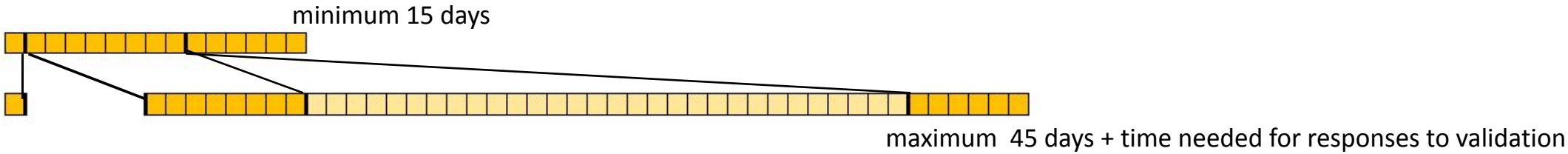
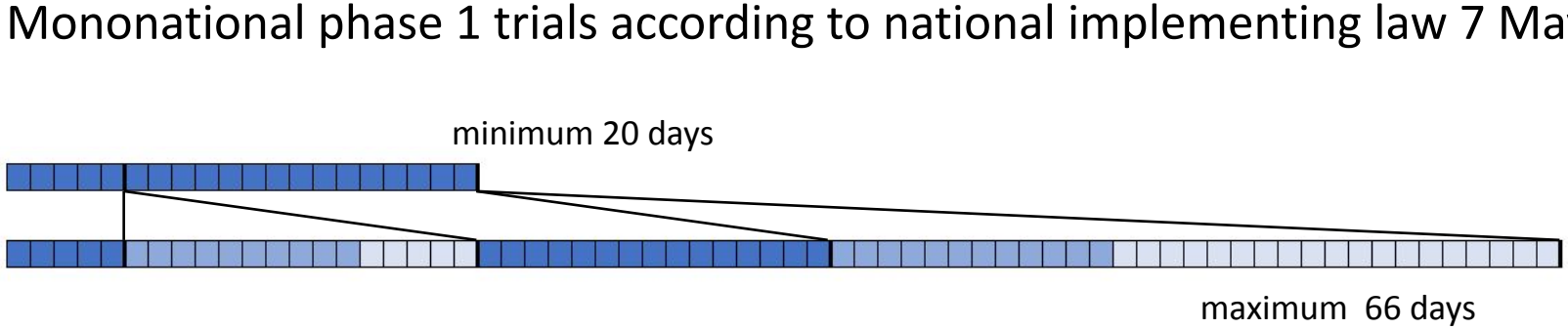
Timelines mononational phase 1 trials

Mononational and monocentric phase 1 trials according to Directive No. 2001/20/EC

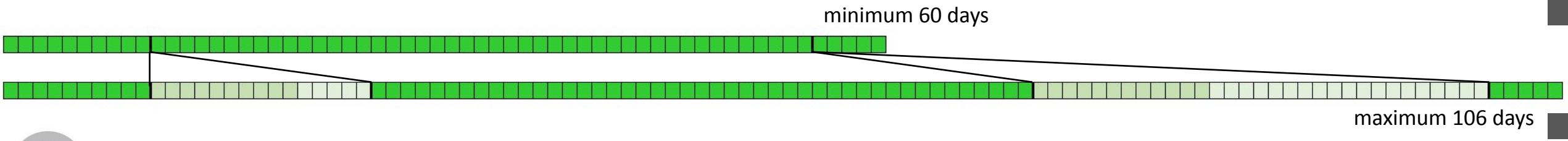


Mononational phase 1 trials according to national implementing law 7 May 2017



+ max 50 days ATMP

All other trials according to CTR



Combined studies – synchronized procedure in BE

Current situation

CTR application

MDR/IVDR application

- parallel applications recommended
- assessment by same independent EC
- no synchronization of timelines

  ↳ approval of different versions of the same documents -> substantial modification needed

Combined studies – synchronized procedure in BE

Synchronized procedure

CTR application

MDR/IVDR application

- parallel application
- assessment by same independent EC
- synchronization of timelines

! VOLUNTARY PROCEDURE THAT NEEDS TO BE REQUESTED BY THE SPONSOR

We believe the synchronized procedure will reduce the administrative burden for the sponsor and prevent delays in the onset of the study due to the approval of different versions of the same documents and subsequent need for substantial modifications to align.

Clinical trials dashboard in BE

IN

OUT

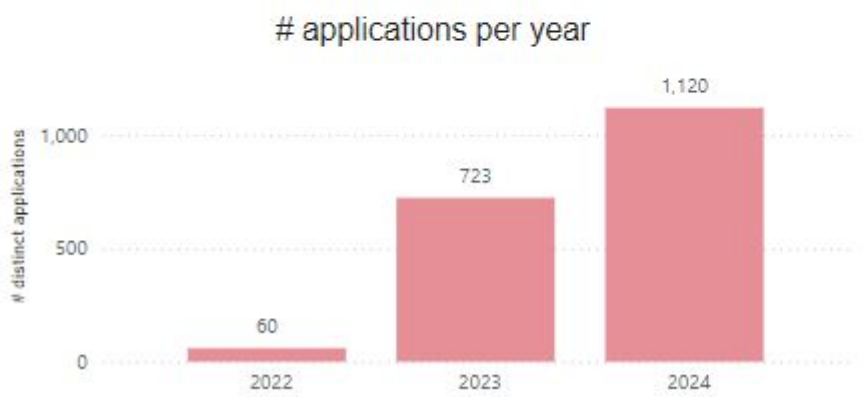
OPEN START

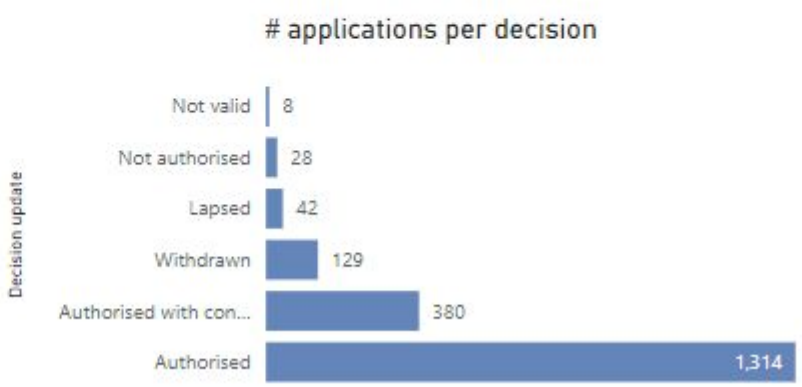
OPEN END

Mean timeline

Timeline mono phase 1

Consofexp





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