First learnings from the European Clinical Trials Regulation and its impact on research in Belgium

Presentation prepared for Immunity for Health

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Clinical trial start-up timelines are a critical element in determining country attractiveness for commercial research

Historically Belgium has been seen as highly competitive for fast activation of new studies

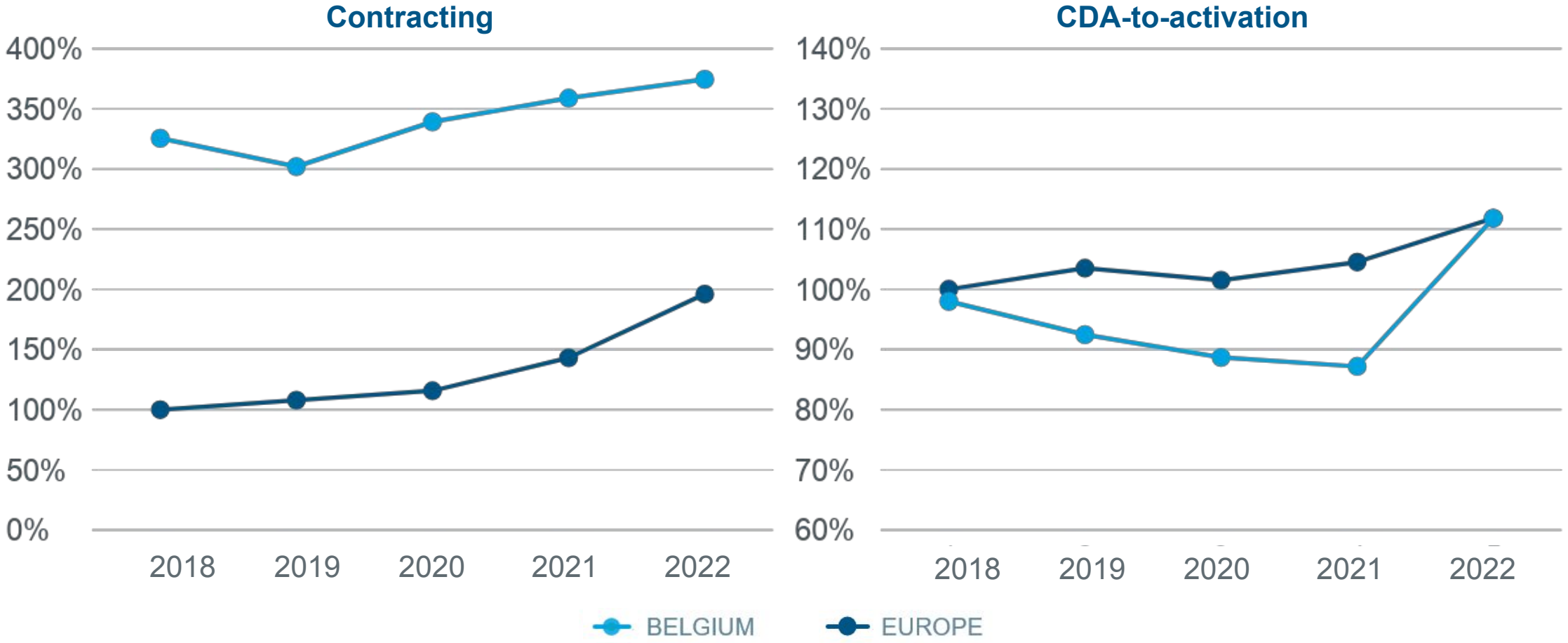
Average rate of Belgium on the following drivers for clinical trial location selection (2017 versus 2022)[11]

Rating scale of 0-10 with 10 being "extremely good"

Source: Deloitte study "Belgium as clinical trial location in Europe" January 2024

Although in Belgium it takes much longer to come to a clinical trial agreement, we have typically been able to activate earlier

Overall, we observe an increase in contracting timelines at European level



Based on IQVIA full-service contracts excluding phase 4 and IQVIA Biotech

Globally clinical trial starts decreased by 15% in 2023, dipping below pre-pandemic level as COVID-19 trial starts slowed

Total number of clinical trial starts by phase, 2014–2023

Source: Citeline Trialtrove, Jan 2024.

Notes: Phase II includes Phases I/II, II, IIa, IIb. Phase III includes Phase II/III and III. Terminated trials are included to track the activity still involved with their initiation, partial execution and termination. Trials were industry sponsored, interventional trials and device trials were excluded.

Report: Global Trends in R&D 2024: Activity, Productivity, and Enablers. IQVIA Institute for Human Data Science, February 2024.

Emerging biopharma companies are responsible for two-thirds of trial starts, but declined the most since the peak in 2021

Share of clinical trial starts by phase and company segment, 2014–2023

Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

Notes: Industry interventional studies phases I,II, III. Company segment when two or more companies are involved is determined by the larger sales segment. Large companies are those with global prescription sales exceeding $10 billion in the calendar year. Mid-size companies have global prescription sales between $5 and $10 billion in the calendar year. Small companies have global prescription sales between $500 million to $5 billion in the calendar year. Emerging biopharma (EBP) companies are defined as those with either R&D spend <$200 million or prescription sales up to $500 million.

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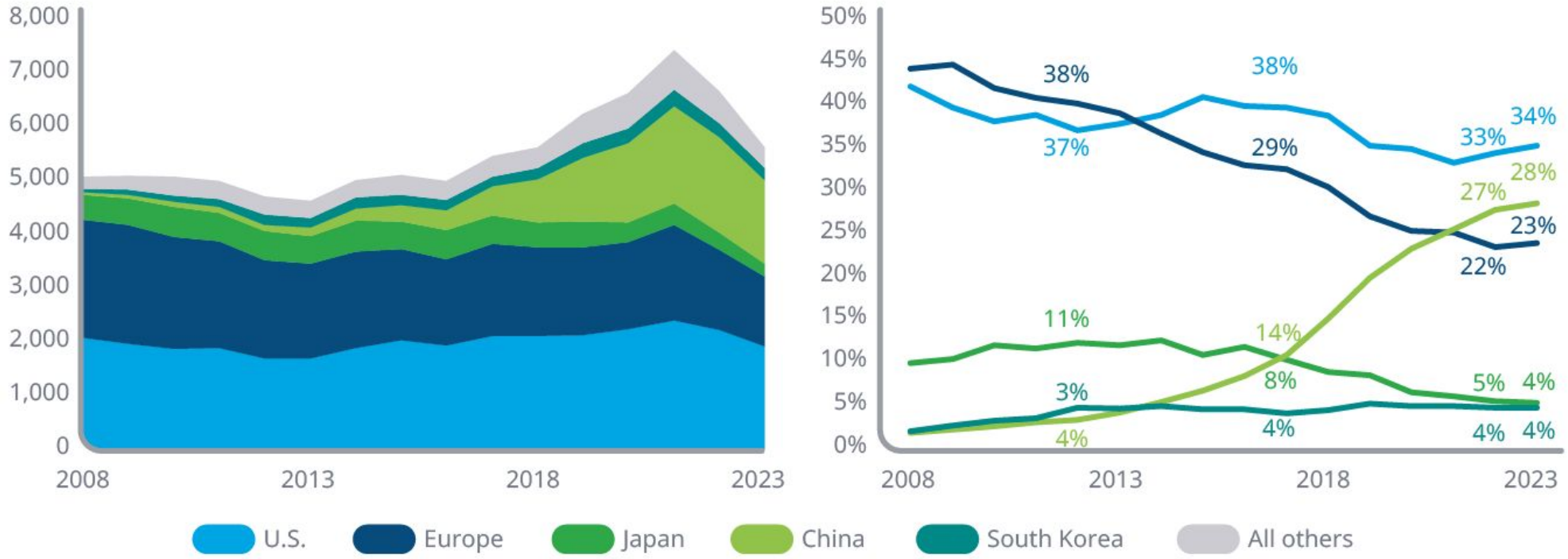
Trial starts from China-headquartered companies have risen to 28% of trial starts from 3% a decade ago

Number of phase I to III trial starts based on company headquarters location, 2008–2023



Source: Citeline Trialtrove, Jan 2024; IQVIA Institute, Jan 2024.

Notes: Includes interventional, industry sponsored trials which are in Phase I to Phase III. Each company involved in a trial is counted individually, so products with more than one company involved are counted more than once and trials may be included in more than one region to reflect their sponsors headquarter geography. Europe is defined as any country in continental Europe. Trial sponsors are subject to variations in company naming and industry consolidation may result in multiple companies being counted individually when they are part of a larger corporate parent.

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In this changing environment, the European Union clinical trials regulation (EU CTR) came into effect two years ago

The original directive dates back more than 20 years

What ?

- Regulation No 536/2014 (“the EU clinical trials regulation”) governs the conduct of clinical trials in the EU and EEA
- Replaced existing EU directive 2001/20/EC

When ?

- Regulation became effective on 31 January 2022 with a 3-year transition period
  - Year 1: regulation is optional for new trials, ongoing trials to start transition
  - Year 2 and 3: all new trials to follow regulation. All ongoing trials to complete transition by end of January 2025

We now have a greater level of harmonization of the rules for conducting clinical trials throughout the EU

Apart from a single submission/decision, focus is on transparency and safety reporting

Main changes

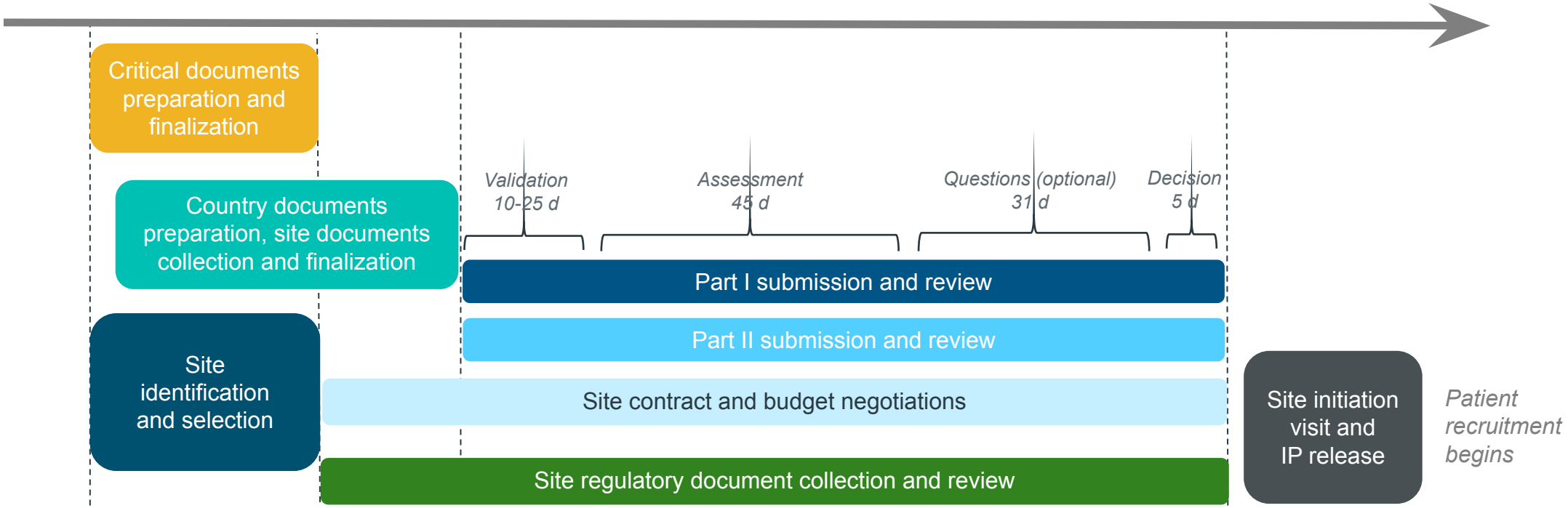
- Standardized clinical trial requirements and assessment timelines across the EU
  - Single electronic submission comprising combined regulatory and ethics assessment
- Increased transparency of clinical trials: more information will be published and become public
  - Protocol, informed consent, milestones, decisions and study results

Regulated system

- The clinical trials information system (CTIS) is a dedicated EU portal and database for submitting information and management of clinical trial lifecycle information
  - Sponsor and authority workspaces
  - Public access

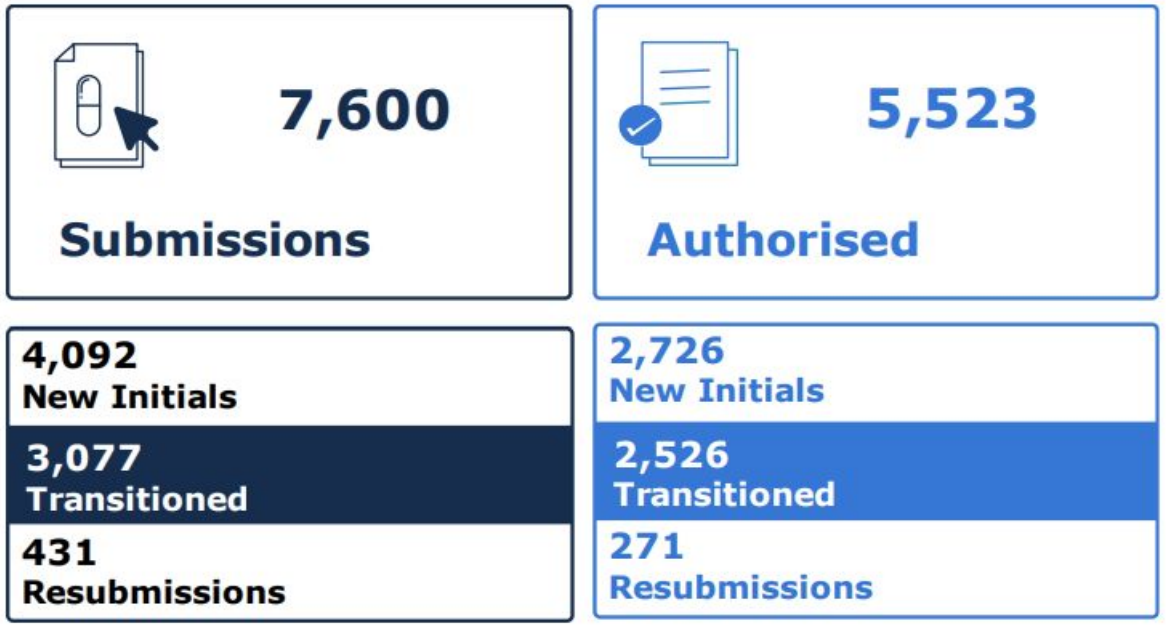
The EU CTR application process takes between 60 and 106 days, depending on the number of questions

Scenario under which part I and part II are submitted in parallel



Two years after the launch nearly 3,000 clinical trials have been authorized, for initial submissions

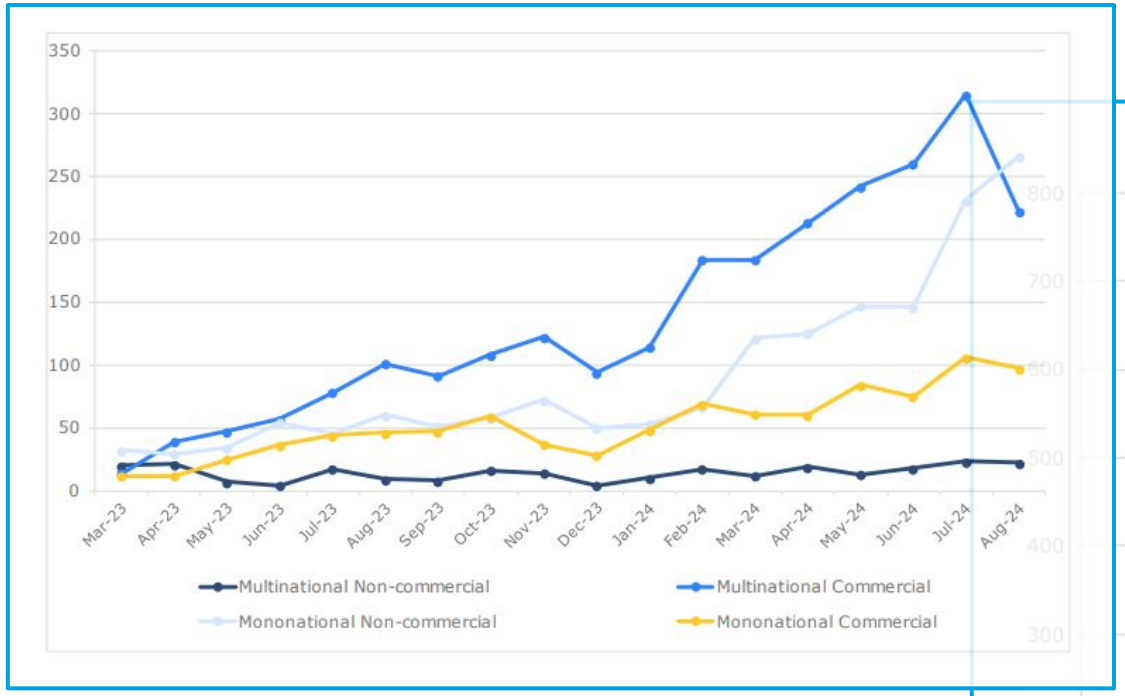
The EMA estimated that between 3,000 and 4,000 trials will need to transition

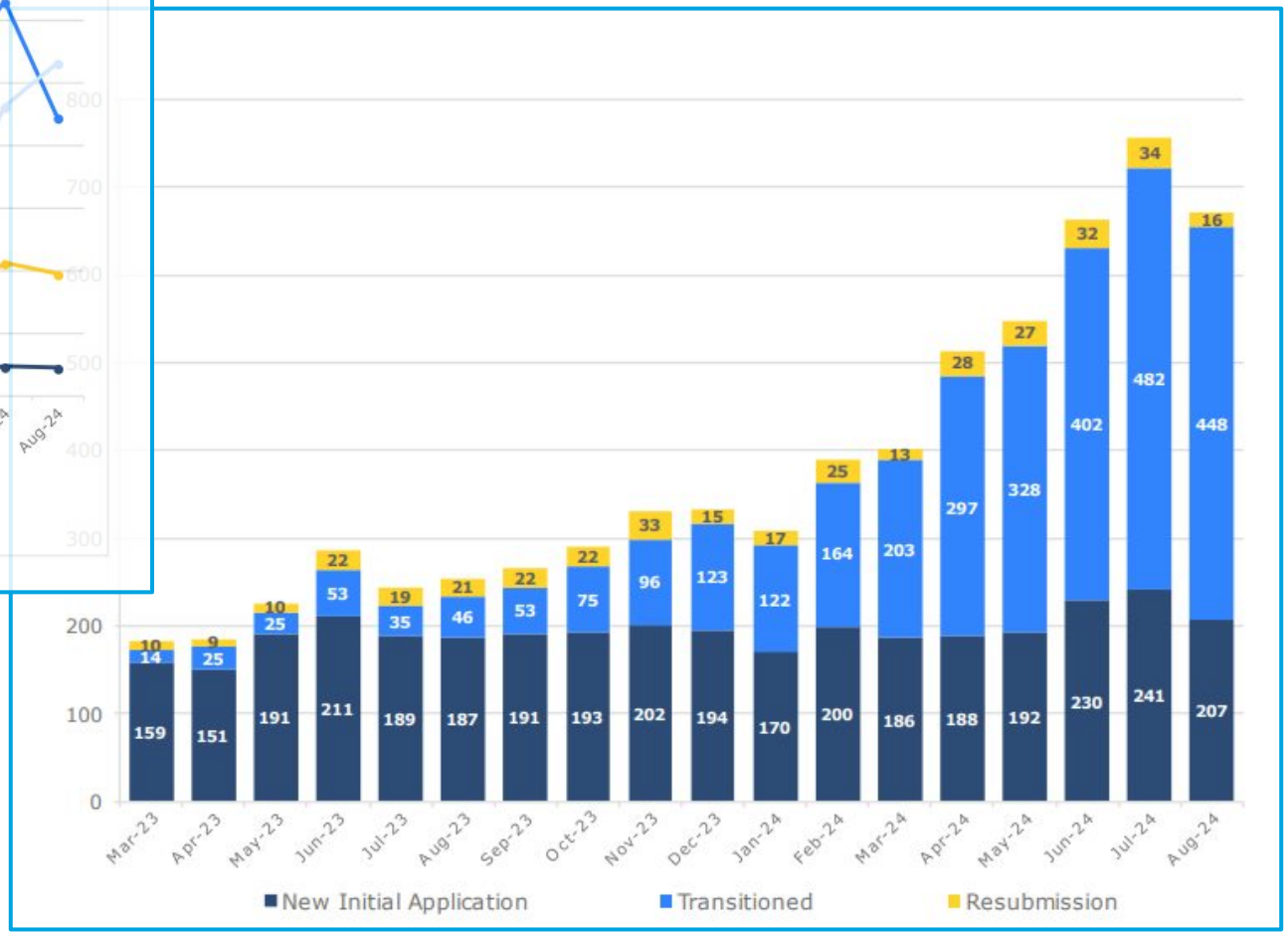


Source: ACT EU KPI report August 2024

Since May of last year, we are seeing a stable number of around 200 new initial applications per month

Multinational commercial studies now represent almost half of this, with average of 6 member states

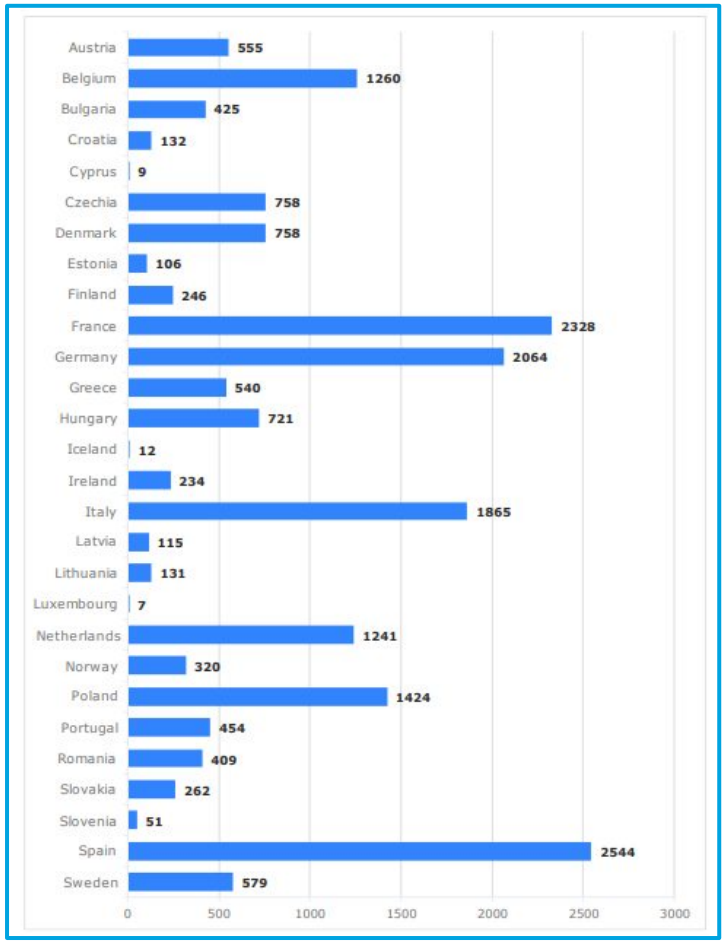


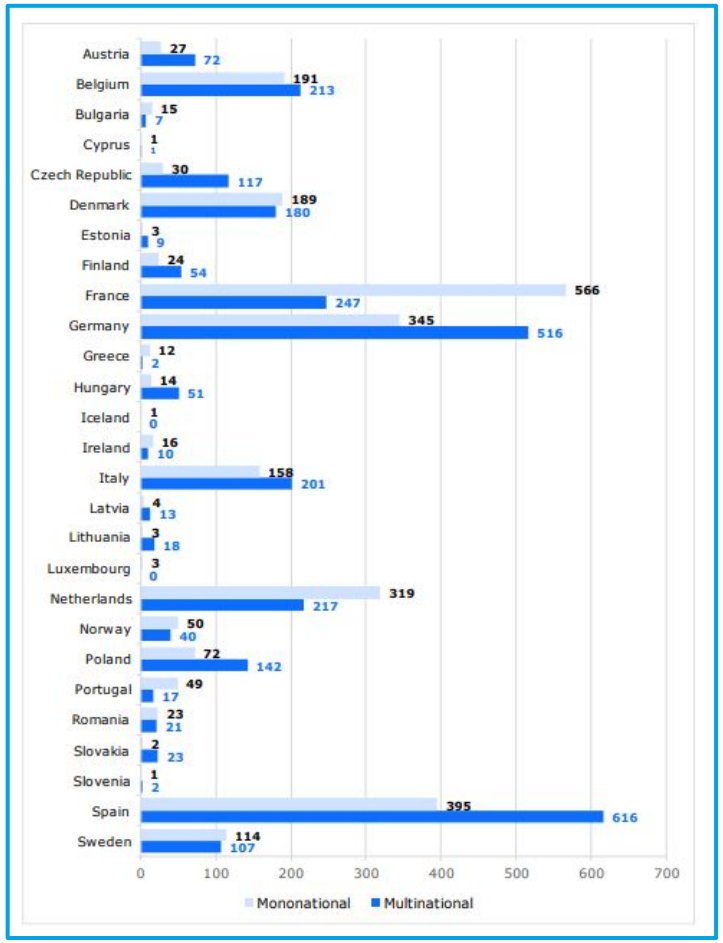


Source: ACT EU KPI report August 2024

There have been more than 1250 studies authorized in Belgium, behind countries with a much larger number of inhabitants

While the FAMHP has been playing an important role as reporting member state





Source: ACT EU KPI report August 2024

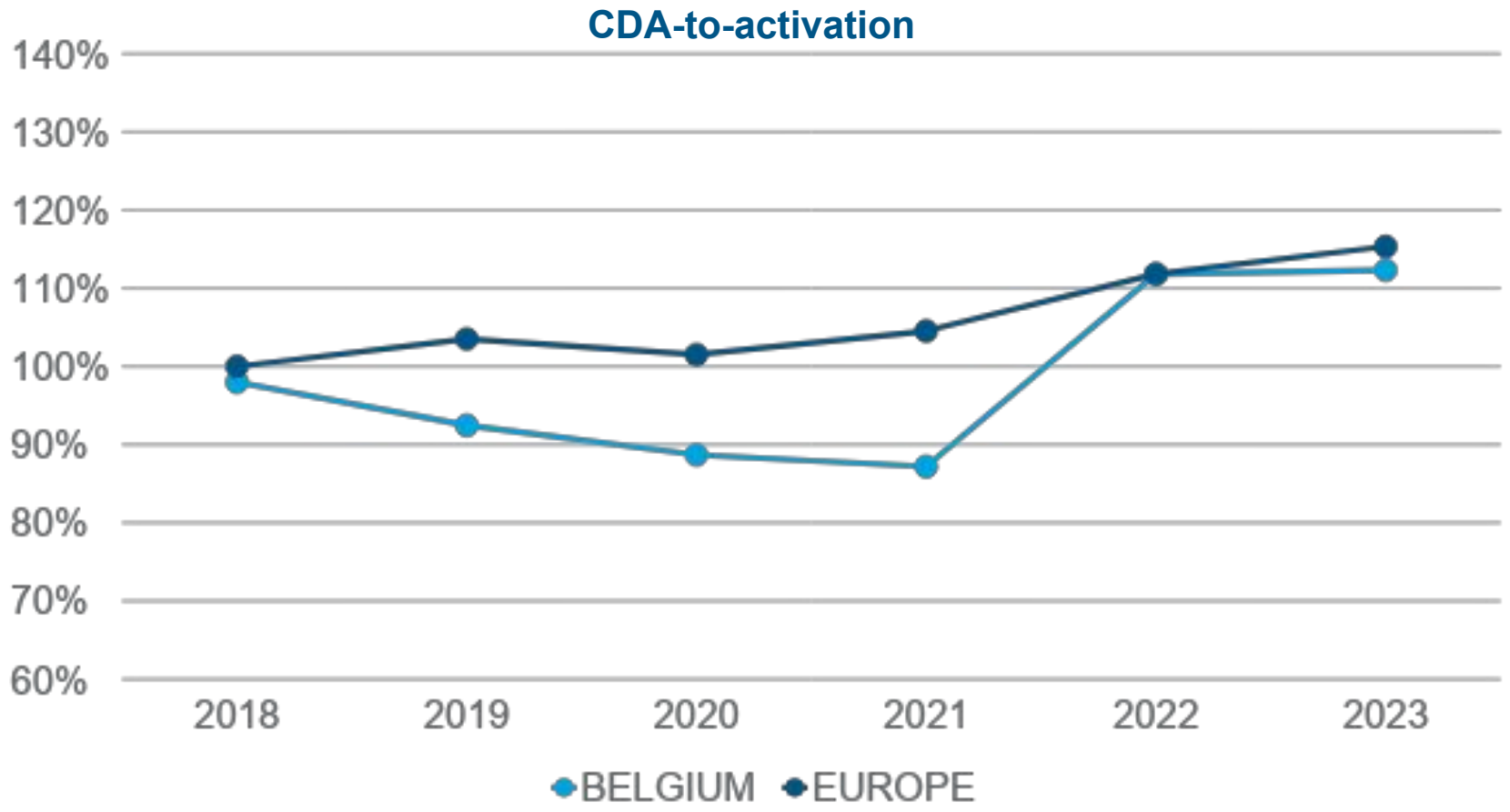
We have several lessons learnt based on 100+ new study submissions and >40 transition trials under EU CTR

Overall EU CTR has now become much more "business as usual"

- General perception
  - Initial concerns about uncertainty of impact on timelines, the functionality of the CTIS, transparency obligations and understanding of the requirements have settled
  - Main concerns of sponsors now relate to CTIS issues, continually updated guidance documentation, inconsistent national requirements and lack of clarity around transition application requirements
- The CTIS portal
  - Many bugs became apparent in the system during 2022, impacting operational efficiencies
  - Challenges continue, but operationally the impact is mainly to increase workload with limited actual delays due to CTIS issues
  - Timelines for assessment very difficult to predict accurately due to the calculations in the system often not reflecting reality

Following the introduction of EU CTR, we see that Belgian activation timelines are more in line with the European average

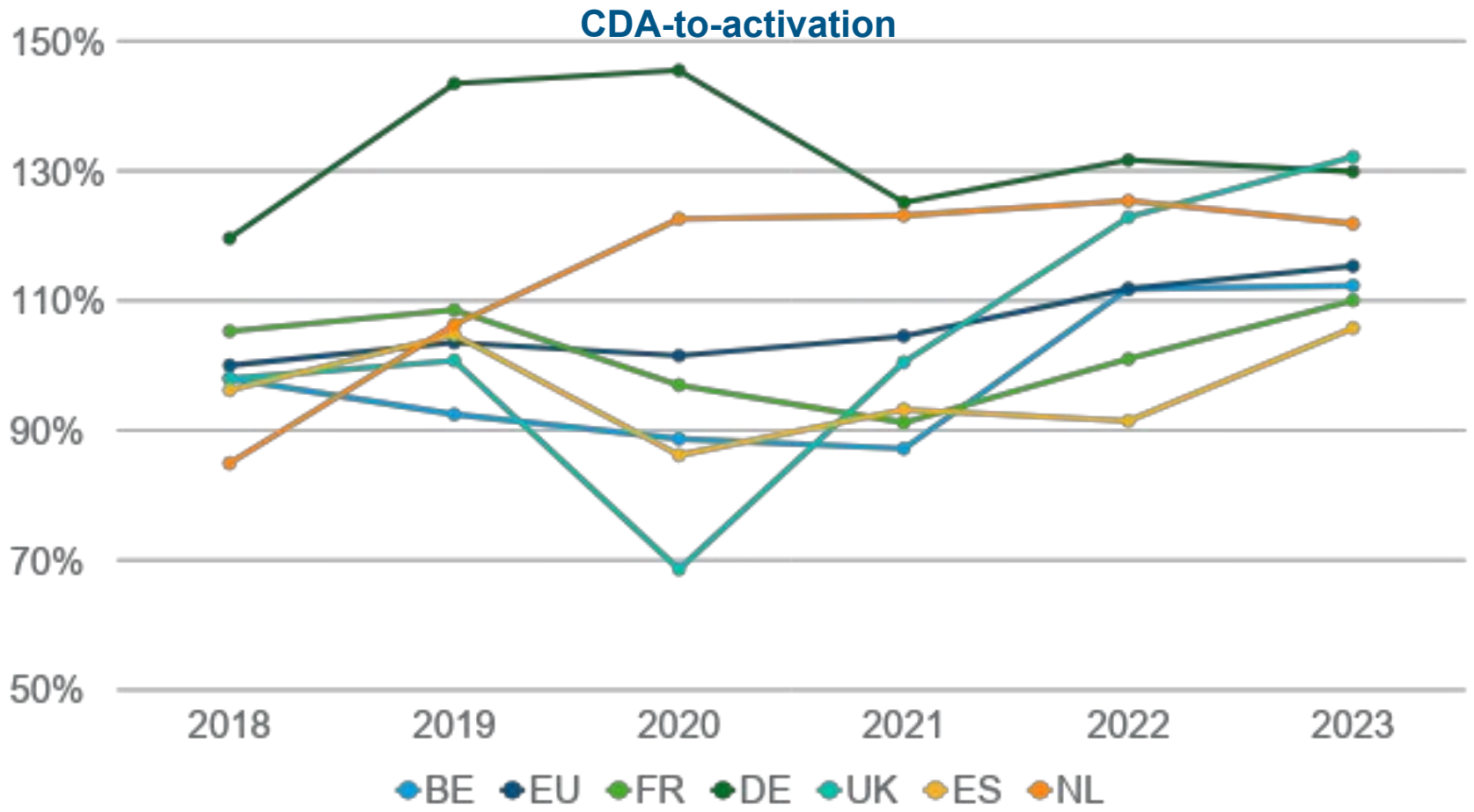
Whereas for the period 2018-2021 we were typically 11% faster



Based on IQVIA full-service contracts excluding phase 4 and IQVIA Biotech

Looking at other R&D countries in our region, major differences in these timelines exist but now seem to narrow

Europe is under pressure to remain competitive versus other parts of the world



Based on IQVIA full-service contracts excluding phase 4 and IQVIA Biotech

In the past Belgium was fastest in our region and second fastest of the 12 largest European countries for clinical research

In 2023 half of the studies submitted are not receiving full approval through the initial submission

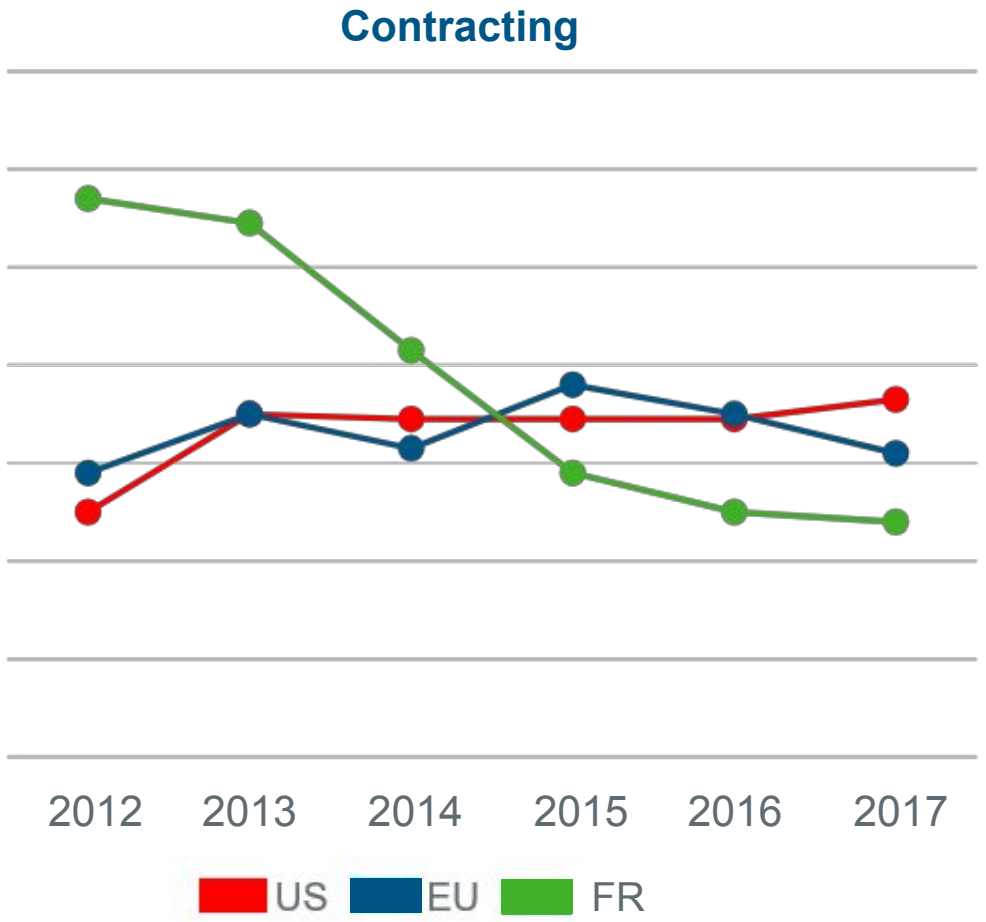
COUNTRY	RANK 18-22	RANK 23	CHANGE
BE	2	6	-4
BG	1	2	-1
CZ	6	7	-1
DE	12	11	0
ES	5	3	2
FR	8	5	3
HU	10	9	0
IT	11	10	0
NL	9	8	0
PO	4	4	0
UA	2	1	1
UK	7	12	-5

Based on IQVIA full-service contracts excluding phase 4 and IQVIA Biotech

Certain elements of this process can be improved locally, potentially resulting in an immediate and significant impact

Change is possible: a case study from France about contracting timelines

- Confronted with a decline in the number of trials, changes have been implemented
  - The “contrat unique” was introduced in January 2014: non-amendable legal text
  - Combined with a central budget negotiation process
- Immediately reflected in the ability to attract new studies



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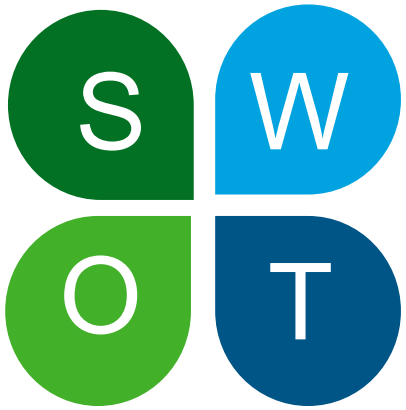
Belgium has traditionally been punching above its weight in the field of clinical research

Now a period of increased change is providing us with both risks and opportunities

Strengths
Well established **ecosystem** for scientific innovation with **experienced** investigators

Weaknesses
Decrease in **large volume trials** due to competition from **lower cost countries**



Opportunities
Research **digitisation** and **clinical technology** disruptions

Threats
Impact of the new **clinical trial regulation** on **fast study activation**

Take-away messages

- Study start-up is a critical process for attracting clinical research
- Belgium used to be and until now remains one of the fastest in Europe
- Growing pains of the regulation currently shield us from full impact
- With the introduction of EU CTR more questions are being raised about including Belgium
- There are new opportunities for building additional strengths
- The French case study shows that change is possible
- It is important to also consider the global picture

Disclaimer slide

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Thank you