Regulatory aspects of the implementation of CTR and work in CTIS: updates and clarifications specific for early phase, tips for a smooth validation

Information sessions for sponsors

FAMHP

Brussels

15.09.2023

Anne LENAERS
DG PRE, FAMHP

famhp
federal agency for medicines and health products

.be

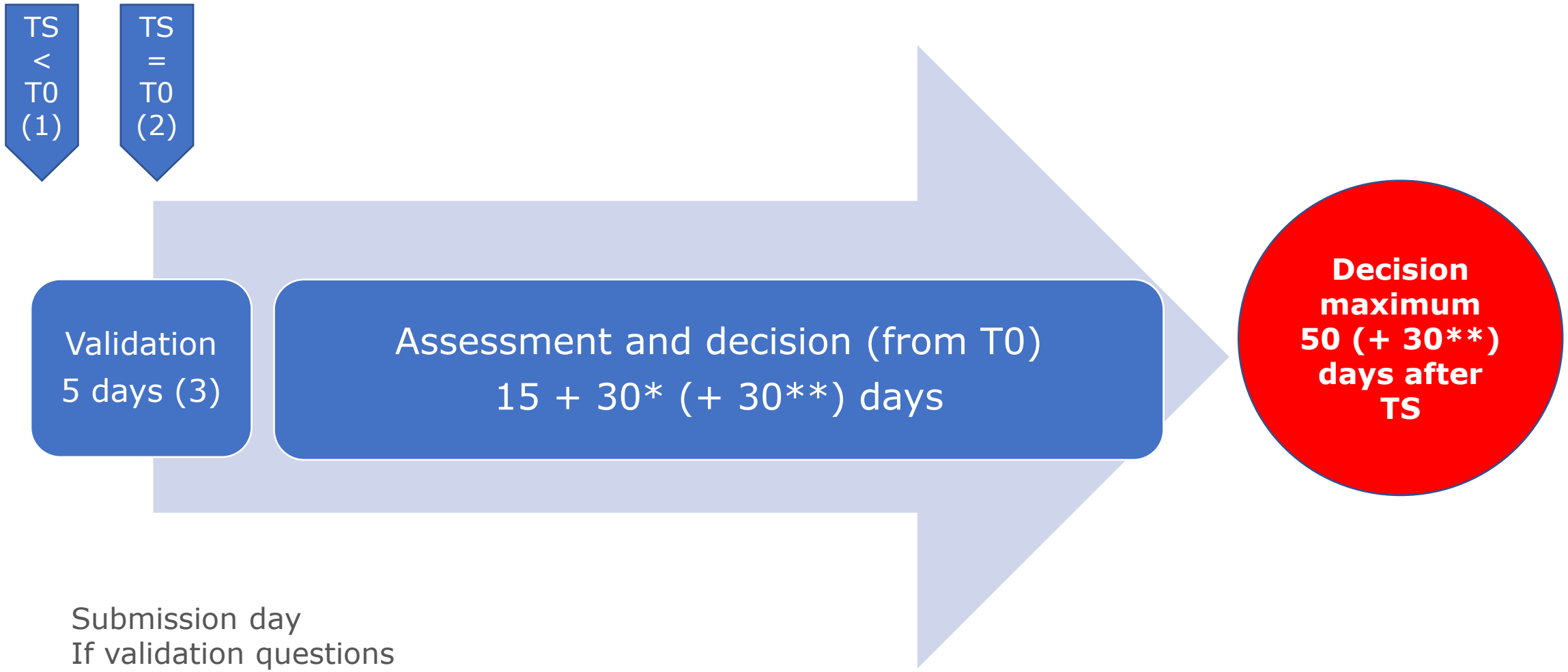
Overview

- Accelerated timelines for mono-national phase I trials in Belgium
- New information and updates
- Reminder
- Regulatory tips for a smooth validation
- Important links

Overview

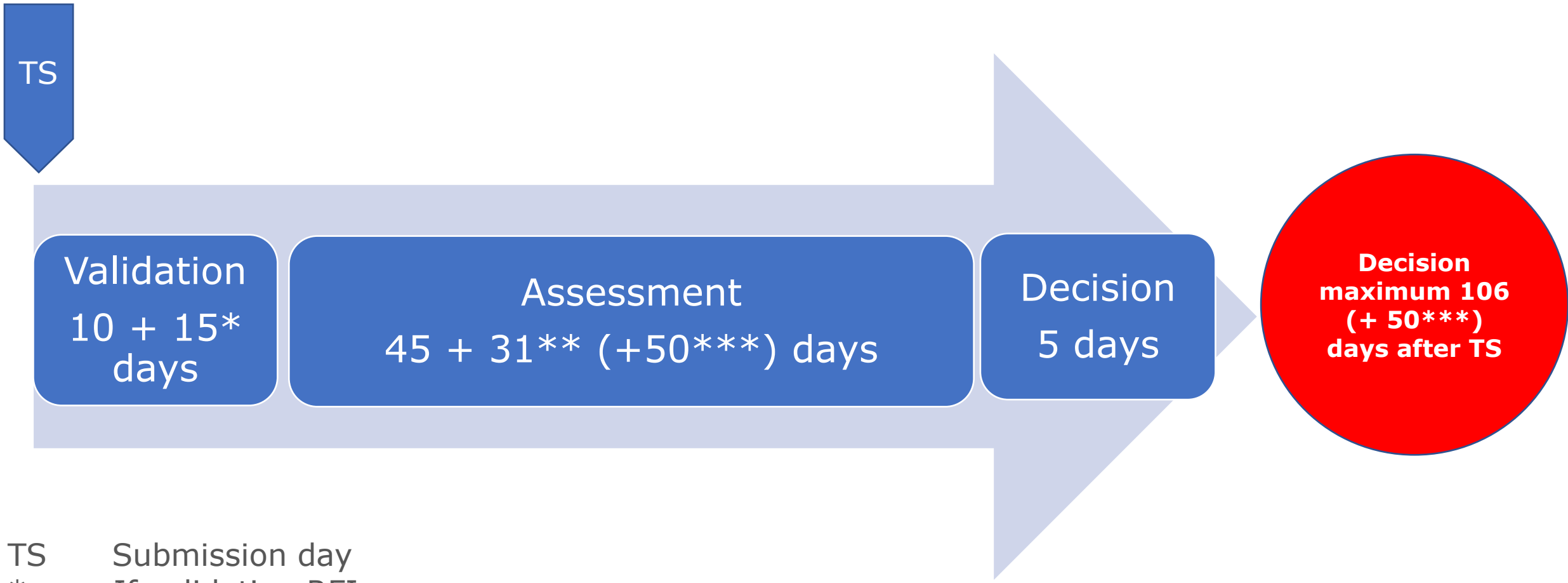
- Accelerated timelines for mono-national phase I trials in Belgium
- New information and updates
- Reminder
- Regulatory tips for a smooth validation
- Important links

Timelines applied for CTD phase I mono-centric trials (law of 7 May 2004)



TS	Submission day
(1)	If validation questions
(2)	If dossier complete from submission
(3)	Estimation of the mean timeline for validation
*	If assessment questions
**	ATMP product

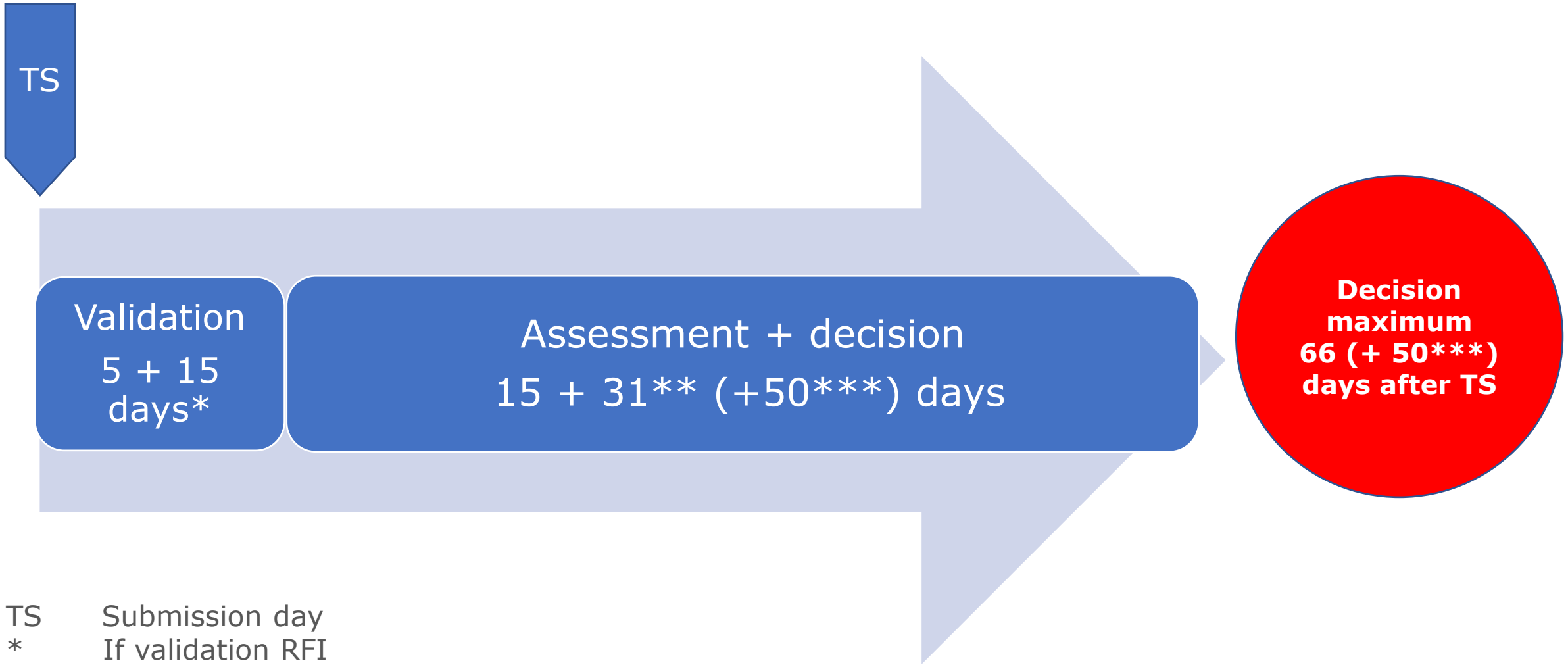
Theoretical timelines as stated in the CTR



TS	Submission day
*	If validation RFI
**	If assessment RFI
***	ATMP/Annex I product

Remark: in practice, these timelines may be prolonged with several days due to application of Euratom rules in CTIS.

Theoretical delay for CTR mono-national phase I trials (law 7/5/2017)



TS Submission day
* If validation RFI
** If assessment RFI
*** ATMP/Annex I product

Comparison

Phase I mono-national delays according to the different legislations:

Actual timelines for CTR mono-national phase I trials

- Maximum timeline (law 7 May 2017):
  - 20 days if no validation and/or assessment RFI;
  - 66 days if validation and/or assessment RFI;
  - + maximum 50 days if ATMP/Annex I product.
- 5 days for validation step (+ up to 20 days if validation RFI).
- 15 days for assessment and decision steps (+ up to 46 days if assessment RFI).
- In practice, timelines even shorter with a quick validation and a shortened assessment timeline in case of RFI (less than 31 days added*).
- Most of the time extension for ATMP/Annex I products limited to 30 days.

* The sponsor can shorten timelines as well by answering sooner.

Actual timelines for CTR mono-national phase I trials

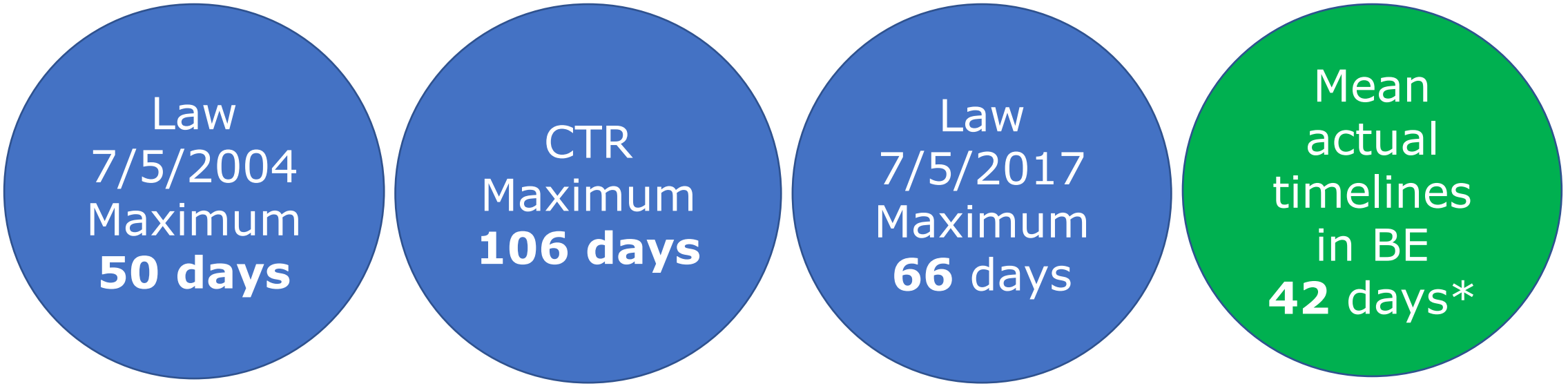
- Mean timeline calculated only for fully completed dossiers (not lapsed nor withdrawn).
- Only for pure phase I mono-national trials.
- 28 mono-national phase I received in CTIS between 31.01.2022 and 31.07.2023.
- None received during winter clock stop.

⇒ For these 28 dossiers, average timeline was **42 days**.

⇒ This is the delay between submission date and coordinated BE decision (EC + FAMHP).

Comparison of timelines

Phase I mono-national delays according to the different legislations **and actual timelines:**



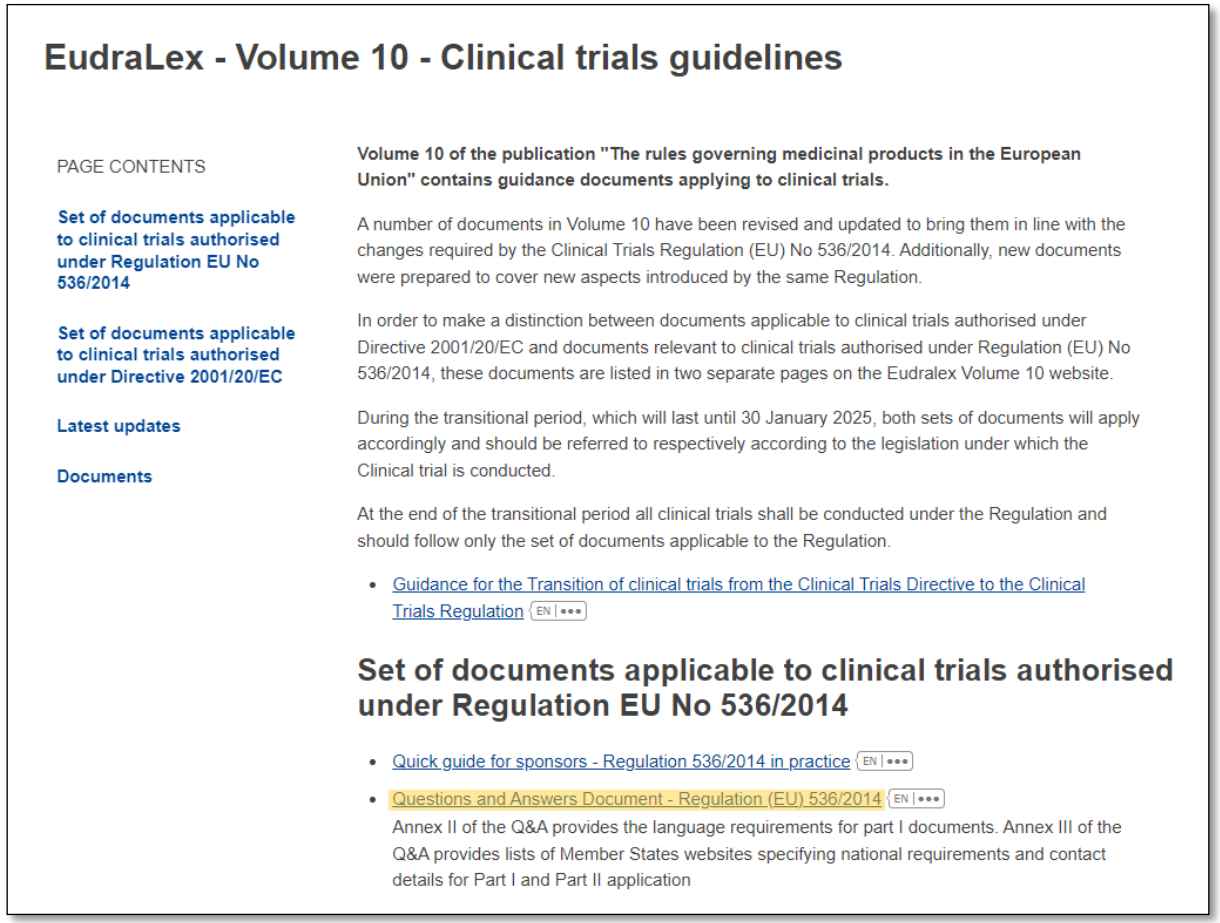
* For pure (non-combined with phase II) phase I mono-national trials (mono or multi-centric).

Overview

- Accelerated timelines for mono-national phase I trials in Belgium
- New information and updates
- Reminder
- Regulatory tips for a smooth validation
- Important links

CTR Q&A in Eudralex volume 10

- New version 6.5 published on 19 July 2023.
- Deletion of chapter 11 on transition trials.



EudraLex - Volume 10 - Clinical trials guidelines

PAGE CONTENTS

Volume 10 of the publication "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.

A number of documents in Volume 10 have been revised and updated to bring them in line with the changes required by the Clinical Trials Regulation (EU) No 536/2014. Additionally, new documents were prepared to cover new aspects introduced by the same Regulation.

In order to make a distinction between documents applicable to clinical trials authorised under Directive 2001/20/EC and documents relevant to clinical trials authorised under Regulation (EU) No 536/2014, these documents are listed in two separate pages on the Eudralex Volume 10 website.

During the transitional period, which will last until 30 January 2025, both sets of documents will apply accordingly and should be referred to respectively according to the legislation under which the Clinical trial is conducted.

At the end of the transitional period all clinical trials shall be conducted under the Regulation and should follow only the set of documents applicable to the Regulation.

- Guidance for the Transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation EN •••

Set of documents applicable to clinical trials authorised under Regulation EU No 536/2014

- Quick guide for sponsors - Regulation 536/2014 in practice EN •••
- Questions and Answers Document - Regulation (EU) 536/2014 EN •••
  Annex II of the Q&A provides the language requirements for part I documents. Annex III of the Q&A provides lists of Member States websites specifying national requirements and contact details for Part I and Part II application

Transition trials

- A stand-alone document on transition trial has been developed and published on the EU Commission website and on Eudralex volume 10.

- Should be taken into account in conjunction with the following documents:
  - CTCG Best practice guide on transition trials*;
  - template cover letter for transition trials*.

* Both adopted in June 2023 and available on the CTCG website, in section "Key documents list/Guidance".

Transition trials

- This stand-alone Q&A document replaces chapter 11 of the CTR Q&A.
- Introduction message:

The transition of clinical trials from the CTD is an administrative process following which the assessment by MS is reduced to the minimum required to ensure compliance with the CTR rules (i.e. transparency, trial category).

As a matter of principle,

- what was already assessed will not be reassessed;

- no update of templates is needed; and

- no need to retrospectively create a site suitability form.

Clinical trials will be considered regulated by CTR when they will be authorised under the CTR by a first MS on the basis of a transition application.

Transition trials

- Only CTD approved documents accepted.

- No document that was not previously approved, except for consolidated protocol (according to the CTCG best practice guide for sponsors).

- CTR rules apply as soon as first authorisation issued in CTIS.

- Even if CTD protocol submitted, not yet CTR worded (e.g. in relation to serious breaches), CTR notifications rules apply from that first authorisation.

Transition trials

- All clinical trials authorised under the CTD with at least one active site in the EU on 30 January 2025 need to be transitioned and approved under CTR before the end of the transition period

- Sponsors should take into account the time necessary for completion of the authorisation and to submit the application early enough before 30 January 2025

Conditions

CTR Q&A Question 2.8 : What should be understood by conditions?

Proposal for revision of point 102 of this question:

The start of a clinical trial is only possible when the application has been assessed and found to have a positive benefit-risk balance at the time of the authorisation. If not, the application should be rejected. Exceptionally, the sponsor must first fulfil a condition within a defined deadline described in the condition text, e.g. in an approved substantial modification application, which could mean that the start of the trial or the inclusion of the first subject is delayed until the condition is met.

IMPD

Cross reference to IMPD for Sponsors who are not the IMP owner

3 options available in question 2.15 of the CTR Q&A.

First option

A trial sponsored by the product owner (PO) has already been authorised in CTIS.

⇒ A reference to this trial could be acceptable under certain conditions:

- IMP used in a similar population;
- with same dose and route of administration;
- same member states concerned.

> 175. Instead of submitting a complete IMPD in the "daughter" trials, a reference to the "mother" trial containing the approved IMPD could be acceptable under certain conditions. Most importantly, every MSC in every daughter trial has to be a MSC also in the reference ("mother") trial as well. This condition ensures that each MSC in each trial sharing the same IMPD, has the possibility to assess and issue a decision of substantial modifications to the shared IMPD. If this condition is not met, the addition of the reference to the mother trial will be rejected by MSC in the daughter trial. Importantly, Art 14 addition of a MSC to a daughter trial, when the additional MSC is not a MSC in the reference trial will not be possible.

Cross reference to IMPD for Sponsors who are not the IMP owner

Second option

The PO transitions a trial with the same IMP from CTD to CTR.

⇒ A reference to this trial could be acceptable under certain conditions:

- IMP used in a similar population;
- with same dose and route of administration;
- same member states concerned.

IMPD

"IMPD-Q only" application

Third option

No trial with the same IMPD already authorised in CTIS.

Currently no possibility in CTIS to upload an IMPD in the dossier that would not be accessible to the sponsor.

Third option proposed and described at point 129 of the question 2.15 in the CTR Q&A:

- 2 applications submitted in parallel in CTIS;
- new trial submitted;
- PO agrees to submit an "IMPD-Q only" application (Part I only) in parallel;
- same MSCs and RMS mandatory for new trial and "IMPD-Q only" application;
- validation an assessment RFI on IMPD provided to the PO;
- "IMPD-Q only" application not approved and cannot be used for further trials;
- procedure should be repeated for each new application (addition of a MSC, SM or new trial).

IMPD

Clarifications on IMPD-Q only process soon published in the CTR Q&A (question 2.15)

- Full cooperation between PO and trial sponsor required.
- Contractual agreements **should** be in place (bilateral responsibilities and information sharing):
  - A statement by the PO will be requested.

IMPD-Q only

Clarifications on IMPD-Q only process soon published in the CTR Q&A (question 2.15)

GMP documentation and IMPD-Q, sections F & G of annex I of CTR to be provided in the IMPD-Q only application

Labelling of the IMP, section J of CTR annex I, to be uploaded in the “sponsor trial”

For a clinical trial transitioned from the CTD to the CTR with a reference to an IMPD not yet available in CTIS => an “IMPD-Q-only” application should also be done in parallel with the application for transition

IMPD-Q only

Technical tip

To repeat the “IMPD-Q-only” application for the same sponsor trial for a substantial modification or subsequent addition, the product owner can withdraw the initial application and resubmit.

This allows the existing information in the IMPD-Q-only application to be reused and to track the application via the resubmission number (e.g. -00, -01, -02…). This number can then be referenced in the corresponding application in the “sponsor trial”.

Overview

- Introduction to CTR
- New information and updates
- Reminder
- Regulatory tips for a smooth validation
- Important links

CTR article 11

- Part I and Part II not submitted at the same time.
- Part II should be submitted within 2 years from the reporting date (meaning from the conclusion on Part I, not before). If not, trial lapses.
- But no modification of Part I possible before trial fully authorised.
- For multinational trials, if Part II not submitted for some of the MSCs, not possible to submit a SM on Part I before authorisation of the trial in all MSCs.
- Only option if urgent SM: first withdrawal in countries where Part II not yet submitted.

CTR article 11

Substantial modification	SM-3	Part I Part I Part I Part I Part I Part I Part I Part I Part I	BE(Authorised) CZ(Authorised) FR(Authorised) GR(Authorised) NO(Authorised) SK(Authorised) IE(Authorised) LU(Authorised) ES(Authorised)	25/08/2022	08/09/2022	+	+		+ INFO
Initial	IN	Part I & Part II Part I & Part II Part I & Part II Part I & Part II Part I & Part II Part I & Part II Part I Part I & Part II Part I & Part II Part I & Part II Part I & Part II Part I Part I Part I	NO(Authorised with condition) SK(Authorised with condition) BE(Authorised with condition) CZ(Authorised with condition) FR(Authorised with condition) GR(Authorised with condition) HU(Withdrawn) IE(Authorised with condition) IT(Withdrawn) LU(Authorised with condition) ES(Authorised with condition) AT(Withdrawn) DE(Withdrawn) PT(Withdrawn)	19/04/2022	05/07/2022	-	-	-	+ INFO

Overview

- Introduction to CTR
- New information and updates
- Reminder
- Regulatory tips for a smooth validation
- Important links

List of documents for Belgium

List of documents to be submitted in CTIS for Belgium: https://www.famhp.be/en/eu_regulation_5362014
Updated and completed regularly → please always consult the last version on our website.

Contents of a CTR dossier for a clinical trial

The contents of a CTR dossier for a clinical trial are described in Annex I to the Clinical Trials Regulation, as well as in **this document**.

The templates of the application documents in Part II were developed by the European Commission and can be found in Chapter I of EudraLex, Volume 10.

- Recruitment and Informed consent procedure template
- Compensation for trial participants
- Template for declaration of interest by the principal investigator

Information specific to Belgium

In Belgium, there are some special requirements regarding the content of the CTR dossier for clinical trials.

Part I

- Protocol synopsis must be submitted in the three official languages, Dutch, French and German, as a minimum requirement.
- Labels must be submitted in the three official languages: Dutch, French and German, with exceptions as described in the law of 7 May 2017.

Part II

- Required BE template for site suitability.
- The use of these templates is not mandatory, but strongly recommended:
  - Informed consent template for interventional clinical trials of drugs in adult patients (under revision);
  - Template for informed consent for clinical trials of vaccines in healthy adult volunteers ;
  - Curriculum vitae of the principal investigator (developed by the European Commission with BE addendum on specific technical expertise).

Content of the cover letter

According to annex I of the CTR;

- but particularly mention if MD/IVDR, GMO, radiopharmaceuticals involved;
- complete list of IMPs and AxMPs (+ specify registered or not);
- specify if exception to the BE labelling rules (e.g. only English if product administered on site and participants do not deal with);
- specify if the IMP has already been assessed in a CTIS dossier;
- any important/particular aspect on the trial;
- information on where the Reference Safety Information (RSI) can be found.

Signature of the documents

- For BE and most of the MSCs, only 2 documents mandatory to be signed in CTIS:
  - Part I: QP declaration of the qualified person (if applicable);
  - Part II: Site suitability statement(s);
  - 2 versions needed in CTIS, one for publication with signature anonymised and one not for publication with signature visible.
- New templates developed by EU Commission for DOI, Statement of compliance with GDPR: without signature placeholder (available on Eudralex volume 10).
- Cover letter not mandatory to be signed.
- Each time a signed document is provided in CTIS, it must be provided in 2 versions, one for publication and one not for publication.

Naming of the documents

- No date and/or version number should be mentioned in the name of the documents.
- Date and version of the document should be introduced as structured data in CTIS.
- Structured data will be updated at the occasion of the submission of a new version of the document (e.g. substantial modification of the protocol) but name will remain the same in CTIS during whole life cycle of the trial.
- When EU CT number mentioned in the documents, last 2 digits may be omitted.

Naming of the documents

- Best practice on naming of documents published on the CTCG website.
- New V2.0 published since last info session.
- Not mandatory to be strictly followed but helps a lot for smooth evaluation of the dossier:
  - beginning names of documents with letter corresponding to chapter of annex I of the CTR is of great help (downloading CTIS documents puts all Part I documents in one folder and all Part II documents in another folder);
  - please be specific: e.g. name of the investigator or institution in the naming of documents instead of numbers such as CV_PI_001, CV_PI_002, CV_PI_003, … DOI_PI_001, DOI_PI_002, DOI_PI_003, …written statement 001, written statement 002, written statement 003, … ;
  - please provide different names for published document and the unpublished version (e.g. addition of – Redacted in the name of the document).
- Will not result in a rejection if not followed.

Patient facing documents

- To be submitted in Part I.
- At least in the official national language(s) of the region(s) where the trial is conducted.
- EN is optional.
- As stated in annex II of CTR Q&A.
- Some additional patient documents are sometimes requested as part of the Part II RFI.

Transition trials

- The name of the BE CTD EC should be part of the transition dossier cover letter.
- Please consult new guidance documents available on the CTCG website and on the EU Commission website.
- Dossier must be completed at the occasion of the first SM on Part I and/or Part II (except if first SM after transition is a multi-CTs SM).
- No application for addition of a member state will be accepted before the dossier is completed and in line with CTR.
- The subsequent addition of a member state, if applicable, should be announced in the first SM after transition.

Other regulatory tips

Registration in XEVCTM

- Products that cannot be found in CTIS because not yet registered in the products dictionary should first be registered in the Extended EudraVigilance medicinal product dictionary (XEVCTM)
- Purpose is to have a standardised denomination for each product and to avoid multiple entries of a same product
- Information on how to register a product in XEVCTM is available here, in the sponsor handbook and in the EMA substance names best practice (available here)

Other regulatory tips

Answer to the RFI:

- a written answer has to be provided in the RFI section of CTIS for each consideration. Missing or modified/updated documents must be provided in Part I and/or Part II of the dossier which has to be updated by using the update function.

Questions on unclear validation or assessment consideration:

- may be raised to CTR@fagg-afmps.be.

Other regulatory tips

Substantial modifications:

- please clearly indicate what has changed in the dossier and which documents have been updated;
- it is requested to provide track changes and clear versions of updated documents*.

How should the track changes versions be uploaded?

- First the new version of the document intended for publication should be uploaded (this can be a redacted version).
- Then the non-redacted clear version of the document should be uploaded by clicking on the "+" icon (version not for publication).
- Lastly, the track changes version of the non-redacted version of the document should be uploaded by clicking again on the "+" icon (several documents may be uploaded as not for publication).

* Also applies when modified documents are provided as answers to RFI.

Overview

- Introduction to CTR
- New information and updates
- Reminder
- Regulatory tips for a smooth validation
- Important links

Important links (Updated)

- Clinical Trials Regulation 536/2014.
- CTIS online modular training program.
- New sponsor's quick guide published on Eudralex volume 10 (version 2.0 published on 21 March 2023 available at the top of Eudralex volume 10).
- CTIS Sponsor handbook (new version 3.02 dated 11 April 2023 published).

Important links (Updated)

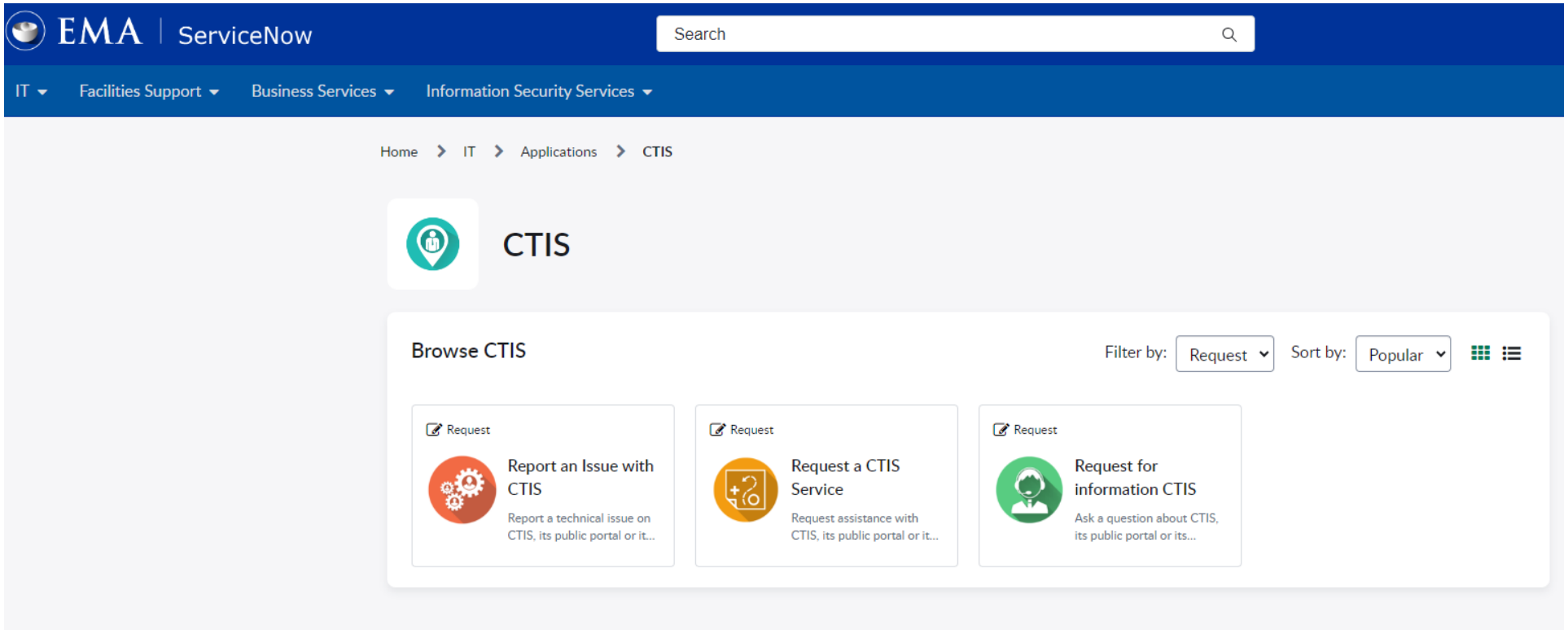
- **Protection of Commercially Confidential Information and Personal Data**
  - Guidance document (and its annexes) updated to V1.1 on 10 July 2023 and Q&A.
  - Should be read in conjunction with ACT EU Q&A on CTIS transparency aspects (new version 1.2 published on 16 May 2023).
- **How to be kept informed of CTR/CTIS important/new information?**
  - Subscribe here to receive the Clinical Trials Highlights Newsletter and newsflash published by EMA.
  - Follow this link for list of known issues in CTIS, release notes and planned system interruptions.

Important links (Updated)

Move of CTIS User Service to ServiceNow platform

Available at this link

In order to log in, users will need to type in their EMA username followed by @id.ema.europa.eu, e.g. a user with the EMA username "surname_a" should type in surname_a@id.ema.europa.eu.



Glossary

ASR	Annual Safety Report
ATMP	Advanced Therapy Medicinal Product
AxMP	Auxiliary Medicinal Product
CCI	Commercially Confidential Information
CESP	Common Submission European Portal
CT	Clinical Trial
CTCG	Clinical Trials Coordination Group
CTA	Clinical Trial Application
CTD	Clinical Trial Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
CV	Curriculum Vitae
DOI	Declaration Of Interest
EC	Ethics Committee
FAMHP	Federal Agency of Medicines and Health Products
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practices

ICF	Informed Consent Form
IMPD	Investigational Medicinal Product Dossier
IVDR	In Vitro Diagnostics Regulation
MDR	Medical Devices Regulation
MIA	Manufacturing Investigational products Authorisation
MSC	Member State Concerned
NCP	National Contact Point
PI	Principal Investigator
PO	Product Owner
QP	Qualified Person
RFI	Request For Information
RMS	Reporting Member State
RSI	Reference Safety Information
saMS	Safety assessing Member State
SM	Substantial Modification
SUSAR	Suspected Unexpected Serious Adverse Reaction
USM	Urgent Safety Measure
XEVCTM	Extended EudraVigilance medicinal product dictionary

Thank you for your attention!

Questions?

Contact

Federal Agency for Medicines and Health Products – FAMHP

Avenue Galilée - Galileelaan 5/03
1210 BRUSSELS

tel. + 32 2 528 40 00
fax + 32 2 528 40 01
e-mail welcome@fagg-afmps.be

www.famhp.be

Follow the FAMHP on Facebook, Twitter and LinkedIn

Your medicines and health products, our concern

famhp

.be