16.Sept.2022

Regeneron EU CTR Insights

Submitting an Application for a CTA or Substantial Modifications – what do sponsors from outside the EU need to consider

EUFEMED Conference

REGENERON®

TODAY'S REGENERON PARTICIPANTS

Magaly Woolard
Director, Global Study Start-Up

Seán Kilbride, Associate Director, Regulatory Affairs

Rishi Sarna, Associate Director, Regulatory Publishing

Tatiana Constant, Associate Director, Clinical Transparency & Trial Disclosure

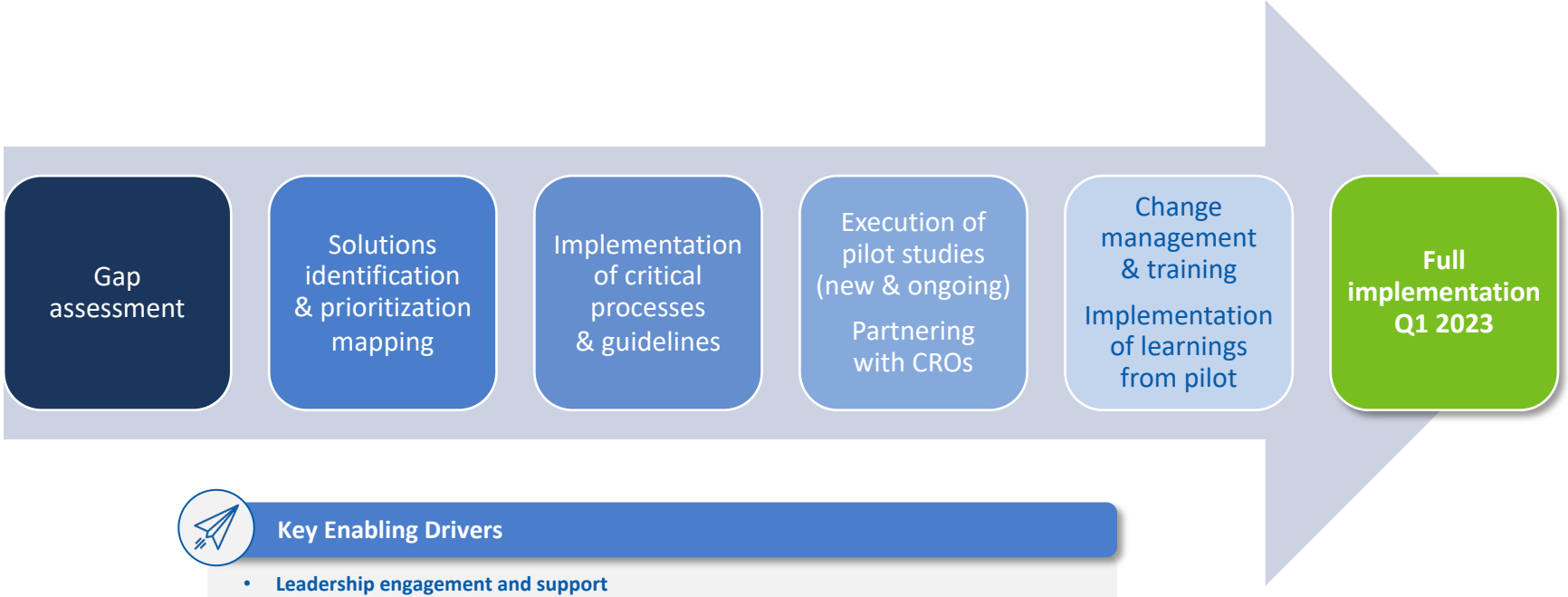
Disclaimer

The views expressed during this presentation are the personal opinions of the speakers.

Regeneron's Implementation Strategy & Plan

REGENERON®

Regeneron High-Level Approach for EU CTR Implementation



Key Enabling Drivers

- **Leadership engagement and support**
- **Continuous engagement of cross-functional teams** – Regulatory, Clinical Trial Management, Study Start-Up, Transparency, Safety, Study Templates, Vendor Management
- **Continuous tracking** of project charter, milestones and pilot program deliverables
- **Change management, communications and training** – Including multiple company-level communications run in parallel, and internal EU CTR web page

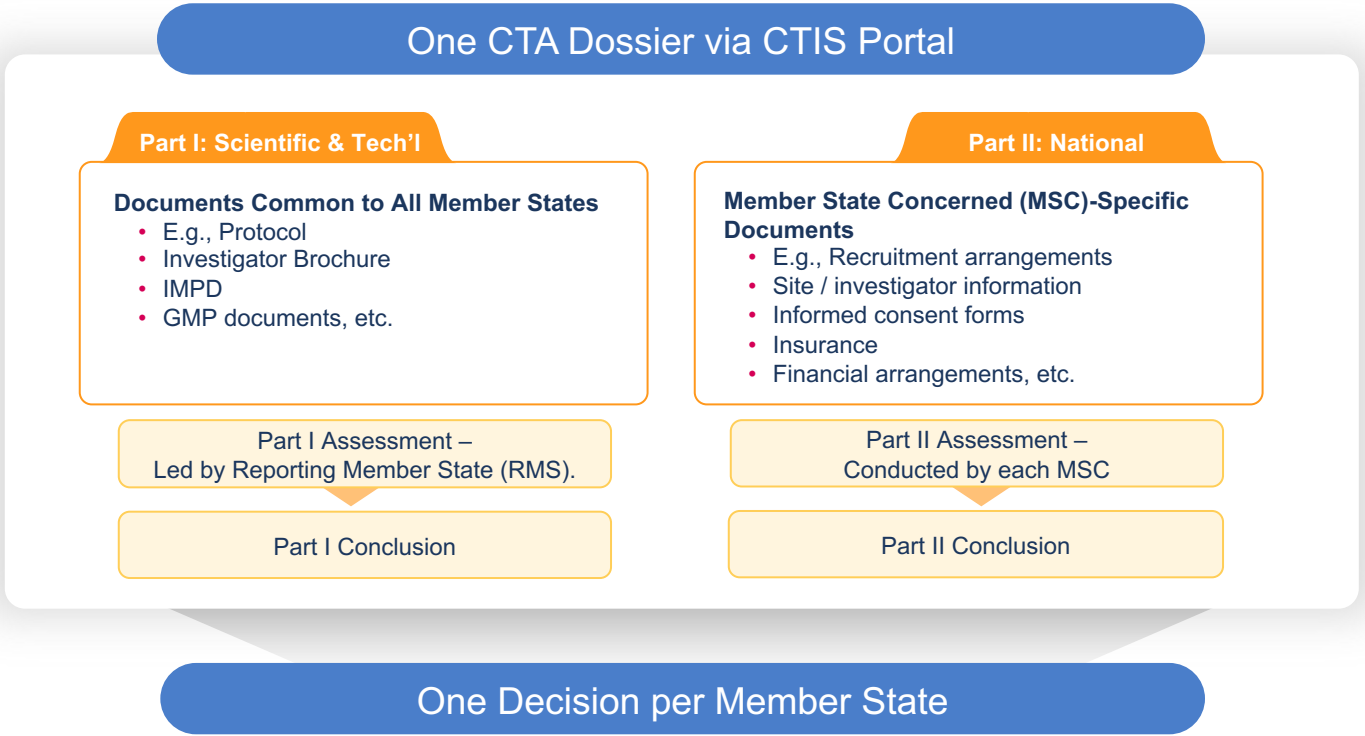
REGENERON®

Part I & Part II Submission Requirements Overview

REGENERON®

Clinical Trial Submission, Assessment & Authorization Process

EU CTR aims to streamline the Clinical Trial Application (CTA) process across the EU/EEA, reducing duplication and delays in the CTA submission and review process



REGENERON®

Part I Requirements Overview

REGENERON®

Regeneron Global Development Infrastructure

Submitting an application for a CTA or Substantial Modifications and what do sponsors from outside the EU need to consider

REGENERON®

Regeneron Pharmaceuticals, Inc.

Tarrytown, NY, USA

- *Clinical Trial Sponsor*

REGENERON® IRELAND

Regeneron Ireland DAC

EU Head Office, including EU Regulatory

- *Legal Representative for CTAs*
- *EU MAH for Libtayo*

REGENERON UNITED KINGDOM

Regeneron UK

Home to some EU Regulatory staff

- *UK MAH for Libtayo*

Partners/Alliance

E.g., Sanofi

- *Sponsor for some EU CTAs*
- *EU MAH for Dupixent*

Regeneron & EU CTAs

EU Clinical Trial Regulation facilitates direct submission of EU CTAs to EU/EEA Member States through CTIS by Regeneron

EU Clinical Trial Directive

- EU Regulatory team responsible for leading **National Competent Authority (NCA)** submissions/responses to requests, etc.
- Clinical team responsible for leading ethics submissions/responses to requests, etc.
- Mono-national studies could be submitted directly to NCA/ethics by Regeneron
- CROs used for multi-national studies
  - Submissions to NCA and ethics
  - Compliance with any additional local requirements & translations
- EU Regulatory team submitted Voluntary Harmonisation Procedure CTAs for multinational trials in advance of EU CTR

EU Clinical Trial Regulation

- EU Regulatory team responsible for leading **Part I** submissions/responses to requests, etc.
- Study Start-up team responsible for leading/overseeing Part II submissions/responses to requests, etc.
- Mono-national **and multi-national CTAs** will be submitted directly to Member States via CTIS
- CROs used for Part II in multinational studies

Preparing for Part I Documents Collection & Processing

Regeneron EU Regulatory Team

- **Prepares "Form", "MSC" and "Part I" sections in CTIS**
  - Part I documents are gathered from functions across the organisation, e.g.
    - Protocol & Investigator's Brochure: Medical Writing
    - IMPD and GMP documents: Chemical, Manufacturing and Control Regulatory Sciences & RA CMC Liaisons
    - Label: Clinical Drug supply
- **Proposes RMS**
- **Submits Part I** or **Part I + Part II**

Notably, Regeneron used the VHP for most multinational trials

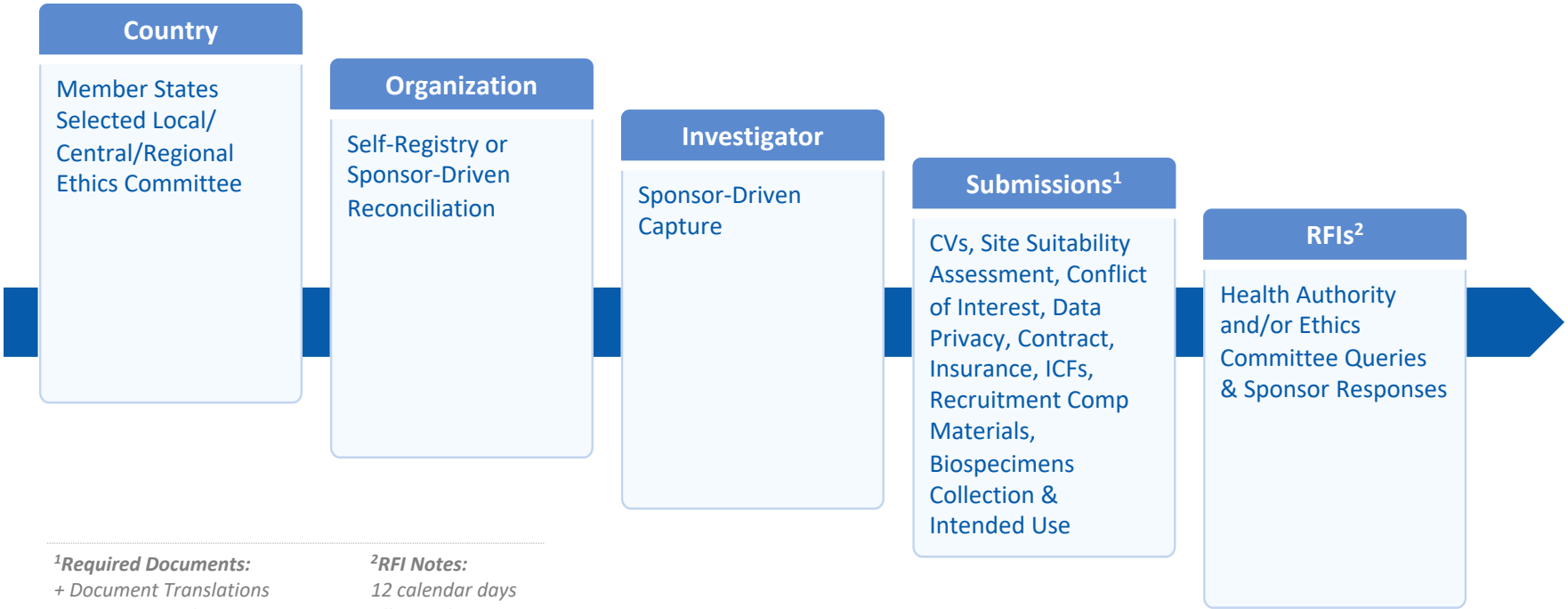
- Some **additional requirements**, e.g.
  - Protocol synopsis
  - SPOR and xEVMPD related data
    - Third party vendors
  - Data privacy statement (mandatory document in EU CTIS 'Form' section)
  - Translations, including application form (outlined Annex to EU CTR Q&A)
  - Redactions
  - Deferrals will be applied for (in addition to redaction)

Part II Requirements Overview

REGENERON®

Preparing for Part II Documents Collection & Processing

Member State Requirements

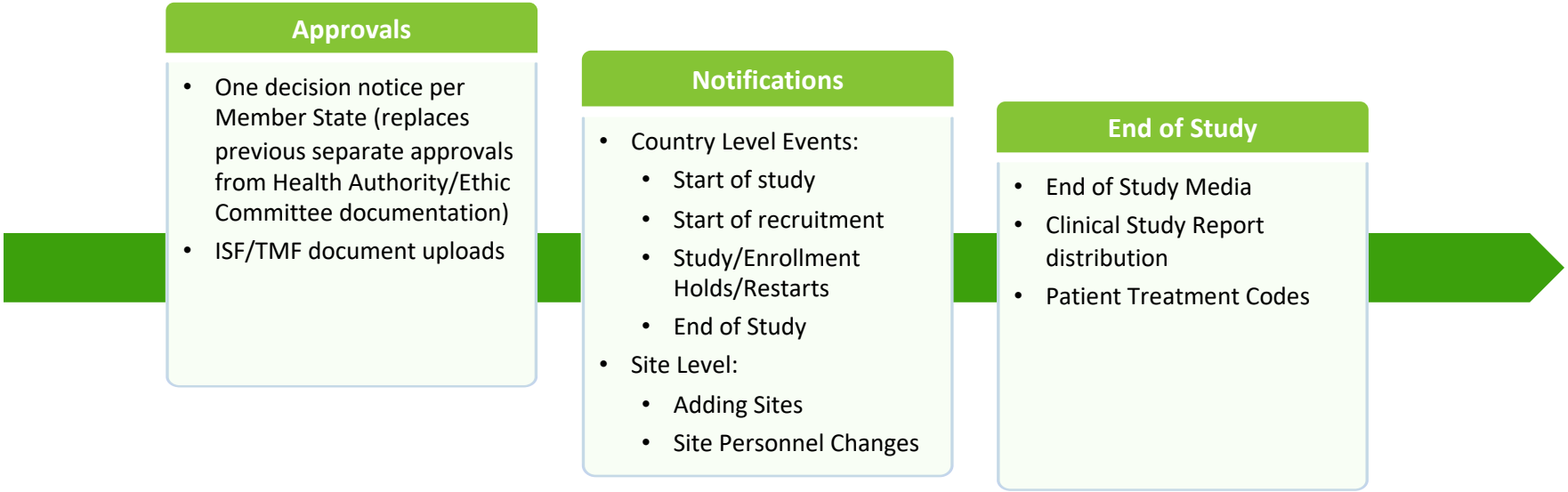


[1]***Required Documents:***
+ Document Translations
+ Document Redactions
+ Publication Status/Designation

[2]***RFI Notes:***
12 calendar days allocated to respond to queries

Regeneron Study Start team responsibilities

Approval and Post-Approval



Regeneron CTIS Readiness

REGENERON®

CTIS Key Facts

CTIS – Clinical Trial Information System

- Portal Go-Live Date Jan 2022
- Single entry point for clinical trial information in Europe
- Increased safety and transparency
- Exchange of information between sponsors and authorities will be fully electronic
- Will offer fully searchable Clinical Trial Information

Sponsor Workspace

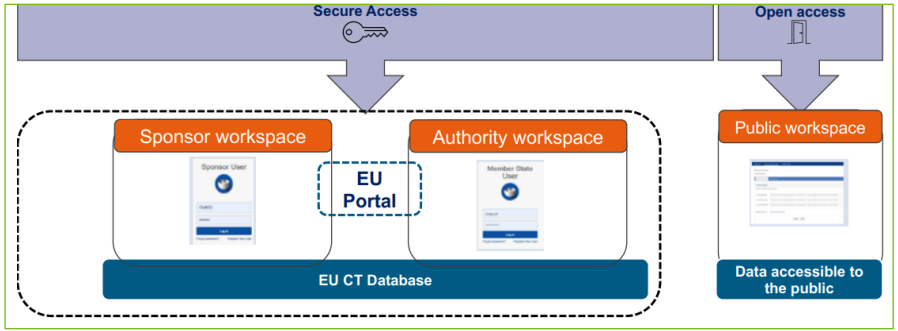
Enables sponsors to prepare and submit applications, trial events and other reporting during the life cycle of a trail

Authority Workspace

Supports the activities of Member States and the European Commission in assessing and overseeing Clinical Trials

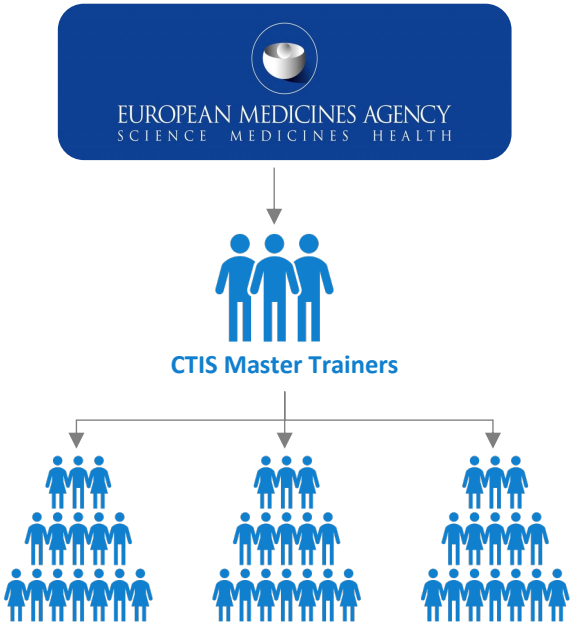
Public Portal

All information that passes through CTIS will eventually be made available to the general public and this can be accessed from the public workspace



REGENERON®

CTIS Master Trainer Initiative



- EMA wanted a streamlined top down training approach and therefore introduced the master training initiative
- CTIS Master trainers are a core group of users who worked closely with the EMA
- Only 1 Master trainer per organisation was permitted
- Master trainers were the EMAs main point of contact for sharing updates, news and training material
- The master trainers participated in instructor led training split across 3 session totally 32+ hours
- Master trainers were responsible for cascading information and training material through their organisation and ensuring CTIS readiness

Regeneron's Approach to Access Management

Organisation Centric Approach

A high level sponsor admin **validated** by the EMA is required.

Suits **medium/large** sized organisations.

Top down approach where users become **affiliated** to the organisation of the high-level sponsor admin.

Approach is **highly recommended** by the EMA.

To create an initial CTA, the CT Admin access needs to be **approved** by the high-level sponsor admin.

Benefits of Organisation Centric Approach

Improves security as CTAs can only be created once user access has been **approved** by the high-level sponsor Admin.

Prevents **duplication** of sponsor organization details

Centralized management of access and Roles especially when working with external parties

How Clinical Trials are set up at Regeneron

Manage access for Regeneron Colleagues

CT Admin
EU Reg Liaisons

CT Admin
Study Start Up

Results Submitter
Clinical Transparency

ASR Submitter
Regulatory Publishing

- Create, populate submit CTA.
- Respond to RFIs
- Submit notifications

Submit End of Trial results

Submit Annual Safety Report

REGENERON®

Regeneron's CTIS Training Approach

CTIS Readiness Training for end users involved a combination of 4 methods

EMA Self-learning Material

End users were assigned curriculum in Regeneron's training portal depending on what role they have in CTIS. Training time ranged from 1-5 hours. All training must be completed before requesting a role in CTIS

CTIS Procedural Documents

Procedural documentation detailed all interactions within CTIS along with roles and responsibilities. End users will be assigned documents to read and acknowledge before obtaining access.

CTIS Supporting Material

Multiple "How To" videos were housed on our internal SharePoint allowing end users to view the videos in their own time. The videos covered a wide range of CTIS functionality.

Sandbox Environment

The CTIS Sandbox environment allowed end users to practice drafting CTAs and gaining confidence before using the live environment.

Key Learnings from EU CTR Submissions

REGENERON®

Regeneron Submission of CTAs under EU CTR

Regeneron has submitted 2 CTAs under our EU CTR 'pilot' stage

One mono-national First in Human to Belgium

- In-house submission (No CRO)
- Monoclonal antibody
- Submitted 28 July 2022
- Validated with no issues on 1 Aug
- Additional time for assessment requested by RMS
- Part I RFIs received 7 Sept (Day 37)

One multi-national transition study to Germany
(no other EU MSC)

- Phase 3
- Submitted 5 August 2022
- EU CTR Q&A guidance followed
  - No new documents prepared
  - Only essential documents submitted
- Validation queries received
- Part I conclusion received 14 Sept (Day 23)

Key Learnings from CTA Submissions under EU CTR

‘Pilot’ Program Implementation

- Implement pilot processes for submission planning & execution under EU CTR
- Gather list of documents required for Part I and Part II application dossiers
- Iron-out internal processes needed to operationalize submission process, e.g., translations, redactions

New Requirements for EU CT Documents

- Revisions of Protocol, IB and ICF to address EU CTR requirements
- New Protocol Synopsis requirements
- New lay language requirements apply to Protocol Synopsis & Summary of Results
- Translation process for CTA documents, and application fields within CTIS Portal

Partnering Externally

(e.g., CROs, collaborators)

- Engage early - ensure appropriate CTIS roles & responsibilities agreed through RACI, process implementation
- Pilot few studies to get experience and pressure test processes/people/systems
- Vendors/CROs need to be registered in OMS

CTIS – 6 Month Review

First submission in CTIS – 28th July 2022

What went well

- Creation of Clinical Trials – streamlined approach using organization centric approach
- SMEs trained in advance
- Plenty of knowledge sharing amongst peers
- Access management organized ahead of time to include backups per trial
- Project management / publishing support
- Sandbox exposure

Issues Faced

- No auto-notifications, so routine monitoring is required to capture any alerts/notices, RFIs, etc.
- Document publishing rules – first version uploaded is automatically published so ensure that it is redacted version
- Renaming documents when uploading into CTIS – Version and date need to match document
- Technical issues faced on day of submission
- Ensure documents are under 10MB - challenging for larger documents like IMPDs – File shrinking, and document splitting is needed
- Products and Substances need updating in XEVMPD in advance, took two days to show up in CTIS even though updated in XEVMPD
- Helpdesk often slow in replying


Thank you!