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The EU Clinical Trials Regulation – Main Changes and Challenges

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Disclaimer

- Carla Gomes, Regulatory Affairs Senior Manager, at PPD, PharmD, MBA; Master in Regulatory Affairs, Expert in Regulatory Affairs by the Pharmaceutical Society, member of the Board of the Regulatory Affairs College of the Pharmaceutical Society

- "The following presentation is intended for educational purposes only and do not replace independent professional judgment. Statements of fact and opinions expressed are mine and, unless expressly stated to the contrary, are not the opinion or position of PPD. "

Summary

Regulatory Strategy in Europe: submission process options, risks and mitigations, best approach for different situation. The EU Clinical Trials Directive versus the upcoming Clinical Trials Regulation: the main changes and challenges.

How authorities are getting ready for the New Regulation and how Pharmaceutical/Companies are preparing themselves. The EU portal and IT constrains. The aim for harmonization, transparency and attractiveness for clinical trials to be conducted in EU.

Agenda

1. Clinical Trials In European Union (EU):
    - EU Clinical Trials Directive 2001/20 EC, 2004
    - Voluntary Harmonisation Procedure (VHP) and VHP plus
    - Clinical Trials Regulation- EU Regulation No 536/2014

2. How is EU getting ready for EU Regulation
    - EMA
    - Member States (Competent authorities)
    - Sponsor/CRO/SME

3. The role of the Regulatory Affairs Professional

Clinical Trials in EU - CT Directive (CTD)

- EU Clinical Trials Directive 2001/20 EC, 2004

Before 2004	After 2004
• 15 different national approaches of MS • Different approval and notification systems • Completely different documentation • Different timelines • Different Languages	• 15/27 MS working with the same English versions of documents: ➢ Investigational Medicinal Product Dossier (IMPD), Protocol, IB, SmPCs, … ➢ First step to harmonize processes and requirements **BUT**
	• Not harmonized: - Assessments - Treatment options and standards - Different document specifications due to different interpretation of guidance docs - Application times at the national CA • increased costs and administrative burdens • Submission to EC and CA in each of the MS

Clinical Trials in EU - VHP Process*

Phase 1 request for VHP and CTA validation (up to 7 days)	• Electronic submission of the VHP dossier to the VHP-C (All general documents i.e. IMPD, IB, Protocol in English) • Validation of dossier and confirmation from each national competent authority to participate in the VHP
Phase 2 CTA Assessment (up to 60 days)	•**Step 1**: review by all NCAs participating in the VHP •If no questions raised, VHP approval at D32 ➔ national step phase 3 •If questions raised, consolidated list of GNAs[1] sent to applicant at D32 ➔ step 2 •**Step 2**: 10 days for applicant to respond to list of GNAs •If revised version of CTA is approvable ➔ Phase 3 •If no unanimous approval at D60 ➔ end of VHP. VHP timelines do not apply for the member states who have unresolved GNAs. •If approval is granted with request for revision of documents at D60, applicant to provide revised documents by D70. •If revised documents are approvable at day 78 ➔ Phase 3
Phase 3 National step (up to 10 days)	• National CTA should be submitted within 20 days after VHP approval • National approval provided by Competent authority within 10 days

*Minimum of 2 EU Member states needed to participate in the VHP, not applicable for EC submissions

[1] GNA Grounds for non acceptance (questions), Data Source: Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications *CTFG//VHP/2013/Rev1June 2013*

Advantages and Disadvantages of the VHP

- The VHP coordinates the assessment of a multinational clinical trial application across the EU.
- A minimum of 2 participating EU Member states are required
- The full VHP process including the national approvals take on average 70-90 days

Key Advantages

- Only general documents in English are required (IB, IMPD, Protocol)
- Consolidated list of questions allowing a single revision of the documents if needed.
- No country specific modifications to the dossier
- If new member states are added and they decide to accept the VHP positive opinion in place, timelines may be shorter (earliest approval day 30)

Disadvantages/Challenges

- VHP is a Competent authority assessment only and does not include the EC
- Voluntary process, therefore countries may refuse to participate
- Short timelines to respond (10 calendar days; no opportunity to request extension of time) if questions raised at the day 30 of VHP assessment period.
- 10 day period for national review (Phase 3) and approvals are not always respected in some countries.

Clinical Trials in EU - VHP Plus

- Gain experience in cooperation/coordinated process between CAs and ECs
- Current focus: Protocol and Investigator's Brochure, RBA.
- No submission of specific documents for EC in VHP Plus i.e. ICF, Insurance, Investigator and sites
- **Ethics committee Involvement:**
  - Contribute to list of GNAs and re-assessment after sponsor response
- **National Step**
  - No reduction in EC standard review timeline since EC documents were not part of VHP assessment
  - Internal agreement that no new GNAs raised at the national step by the NCA
  - All documents approved after VHP should be included in EC submission package

Clinical Trial in EU – EU Regulation N 536/2014

- Regulation on CT that will repeal Directive 2001/20/EC (2004)

- Primary Reasons for the Regulation:
  - **Make EU competitive for clinical trials**
  - Create modern regulatory framework for submission, assessment and regulatory FU and adapt regulatory requirements to practical considerations, constraints and needs without compromising participants' safety, rights and well-being or data robustness
  - Address the global dimension of CT when ensuring compliance with GCP
  - Address issues from Directive 2001/20/EC
    - Lack of Harmonization (28 different sets of guidelines, approval timelines for the same trial varies, different content of CTA, local amendments to protocol)
    - Increased Costs, Delays and Decline in Trial Volume
  - Transparency

- Primary Changes:
  - Simplified Authorization Procedure and Simplified Safety Reporting Procedures
  - Establishes legal basis EC to inspect non-EU countries.
  - Law is structured as Regulation to Harmonize

CTR – DEVELOPMENT HISTORY

- November 2008: European Commission (EC) announces plans for assessment of CT Directive implementation

- February 2011: public consultation on a concept paper for revision of CT Directive 2001/20/EC launched

- July 2012: "Proposal for a Regulation of the European Parliament (EP) and of the Council on CT on medicinal products for human use, and repealing Directive 2001/20/EC" adopted by EC, submitted to Council of Europe and ET

- Regulation approved by European Parliament on 02 April 2014 and Council of Europe on 14 April 2014, and published on 27 May 2014

- Would apply no earlier than 28 May 2016, at least 2 years after publication, linked to the IT infrastructure availability (allows stepwise transposition from Directive to Regulation)

- IT: system ready and available for audit (Aug 2017), EMA agrees system is functional (Dec 2017), EC publishes confirmation in OJ (Apr 2018), application of Regulation (Oct 2018)

CTR – WHAT IS NEW

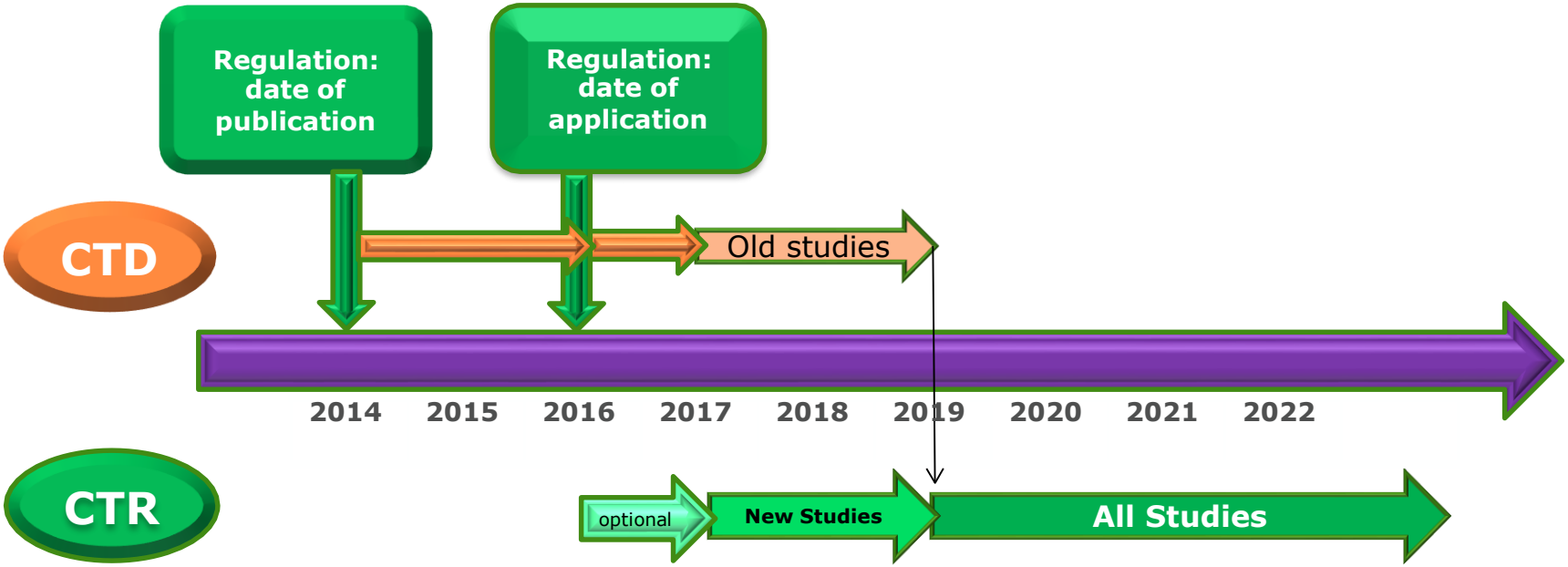
REGULATION!

- Applies in its entirety across EU, no transposition into national laws required (28 countries)
- New IT infrastructure: EU Database & EU Portal
- New simplified application/review procedure
- Improved timelines and flexibility
- Risk-based approach (low-interventional trials)
- Provisions for emergency trials, consenting incapacitated patients, co- sponsorship, serious breach reporting, etc.
- Increased transparency (trial progress, results)
- Focus on informing citizens of Europe (layman language)

Strike the right balance to inform the public, protect public health and foster the innovation capacity of European medical research.

In Bibliography 8

CTR – Plans for implementation



CTR – STUDY SUBMISSION AND REVIEW

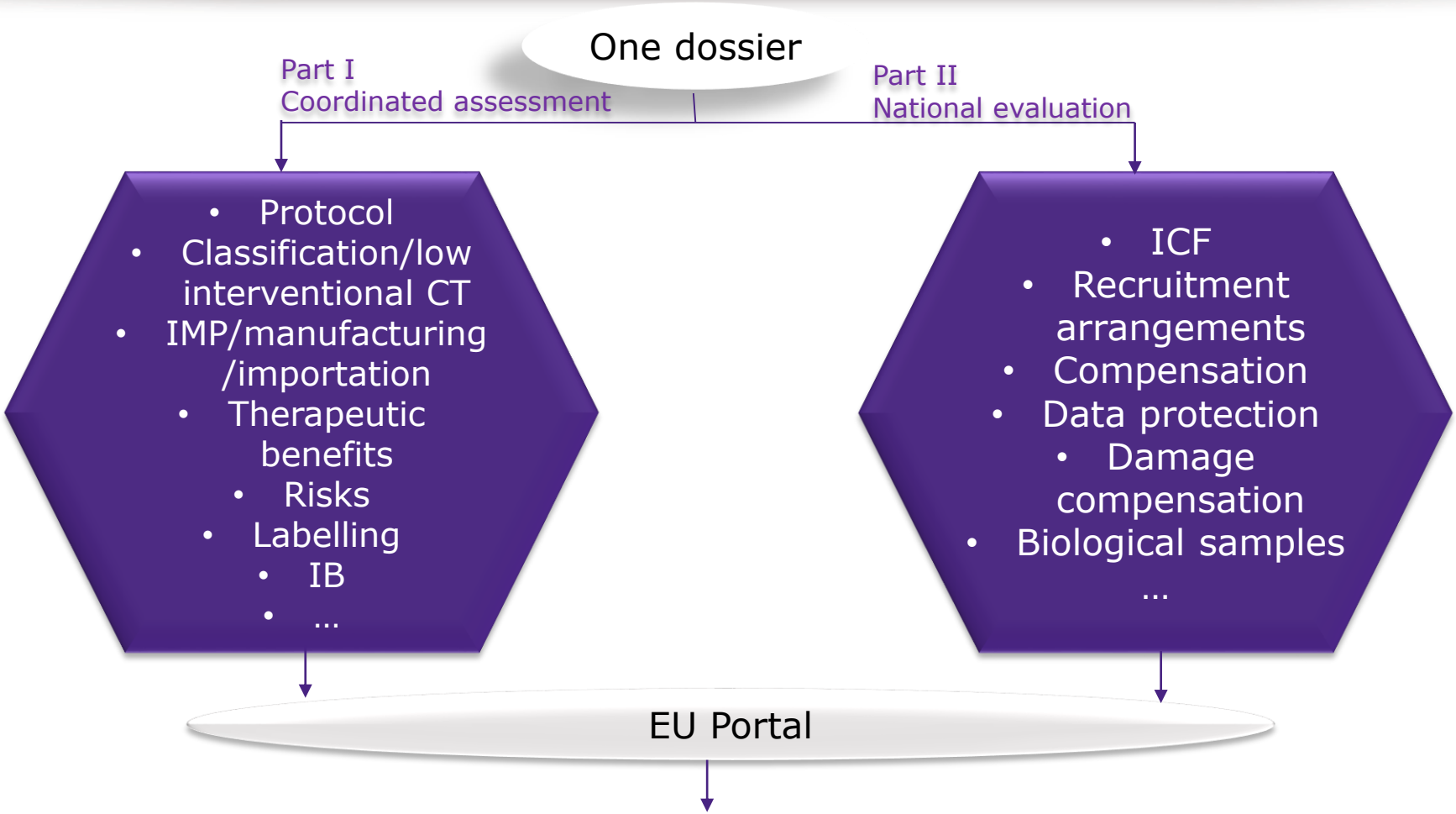
- New simplified submission/review procedure:
  - Single dossier and single submission via EU Portal
  - Documents required for submission listed in Annex I to the Regulation (Annex I & Annex II to replace CT-1 Detailed guidance)
  - Coordinated assessment for multi-state clinical trials
  - Sponsor nominates Reporting Member State
  - Clear timelines, concept of tacit approval

CTR – STUDY REVIEW PROCESS (1)

- Application validation by reporting Member State
- Two-part assessment of the application:
  - ❑ Part I (by reporting Member State in cooperation with other Member States)
    - general aspects (study design and IMP-related aspects)
    - therapeutic and public health benefits
    - risks and inconveniences for the trial subjects
  - ❑ Part II (by each Member State separately)
    - Ethical aspects, country-specific
    - Compliance with country-specific ICF requirements
    - Qualification of PIs and suitability of sites
    - Adequateness of subjects' compensation

- Part I and Part II assessments run in parallel
- Possibility for sequential assessment of Part II after Part I

CTR – STUDY REVIEW PROCESS (2)



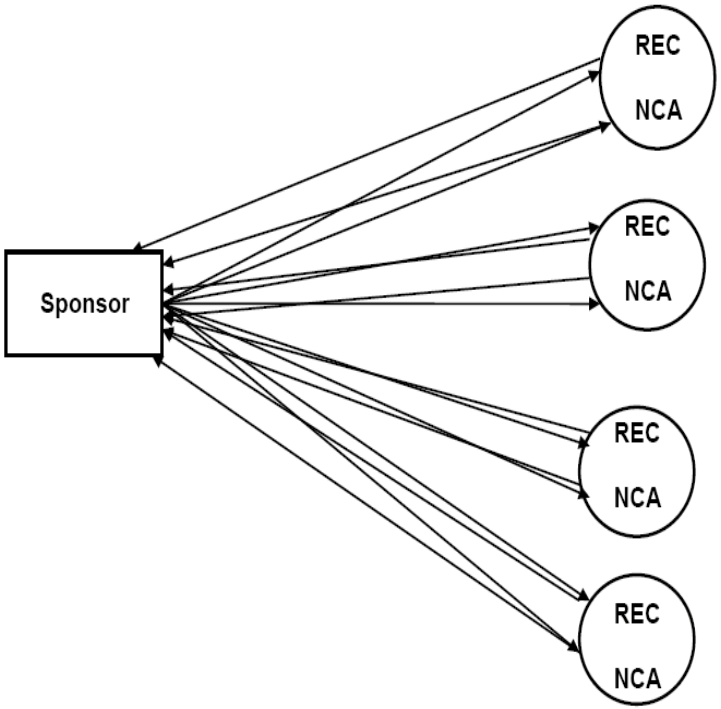
*MSC- Member State Concerned

CTR – IT INFRASTRUCTURE

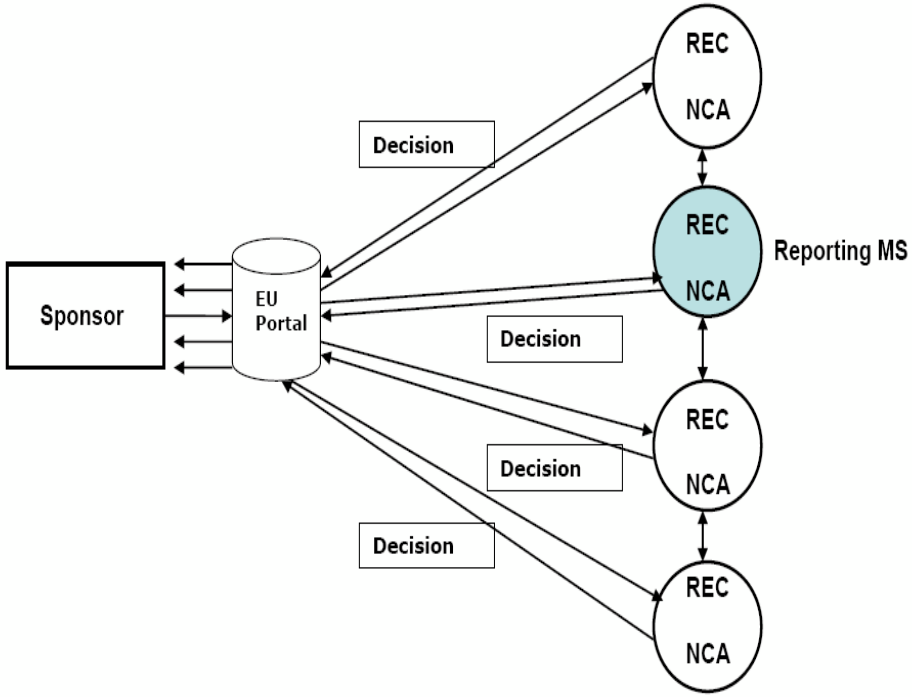
- EU portal and database developed by EMA
- EMA working with MS and European Commission to draw up functional specifications
- "The EU portal shall be technically advanced and user-friendly so as to avoid unnecessary work"
- Full functionality of the database & portal to be verified within 18 months after publication of the Regulation
- Database to enable communication between sponsors and MS, as well as between MS
- Database will be publically accessible
- EU Database user interface shall be available in all official languages of EU

CTR – STUDY REVIEW PROCESS

STUDY REVIEW UNDER CTD:



STUDY REVIEW UNDER CTR:



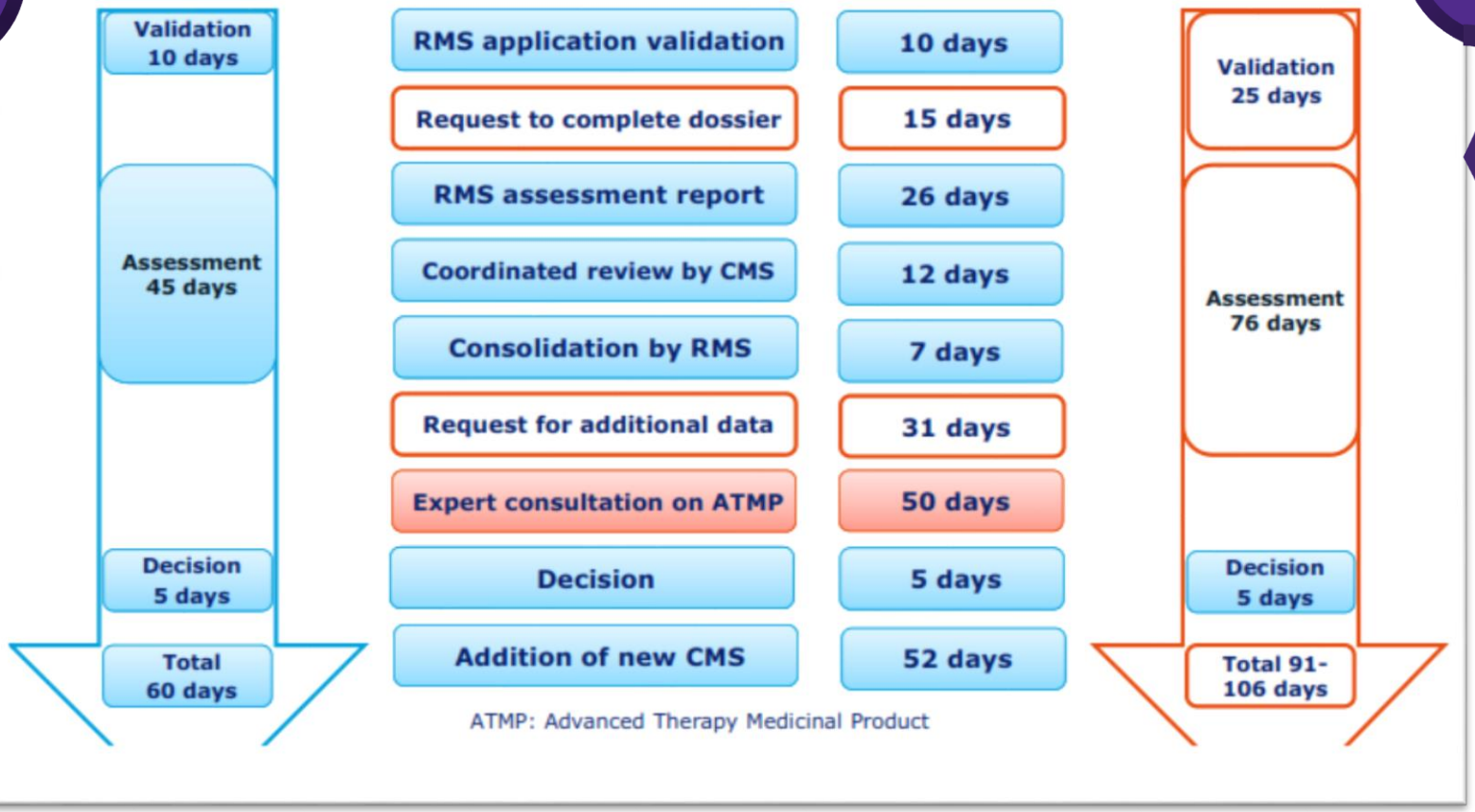
CTR – TIMELINES (IS)

- Initial Submission

CTD

CTR

Review timelines



In Bibliography 6

CTR – TIMELINES (after IS)

Maintenance and EoT

- Notification of the following should be made within 15 days via the EU Portal:
  - Start of the trial in each MS
  - End of recruitment in each MS
  - Re-start of recruitment in each Member State
  - End of a clinical trial in each Member State
  - Global end of a clinical trial

- Summary of trial results + summary for laypersons: to be submitted via EU Portal within 1 year of trial end

- Sponsor shall submit via EU Portal all inspection reports of third country authorities concerning the clinical trial

CTD versus CTR

What Changed	Current: Directive 2001/20/EC (2004)	Proposed Regulation (repeals Directive 2001/20/EC)
CTA Submission Activities 1) Submission 2) Full vs Low	• Multiple National submissions • Interventional = full CTA (60d) even if minor change to standard of care • CSR only	• Single Harmonized Submission • New classification for low intervention study (20d + 20d); adv. therapy (40d + 20d) • Publication of data (FPI, recruitment, final study results)
IT	• Paper or electronic copy depending on country	• Submission Portal
Quality and IMP Guidance	• Defined IMP and non IMP – GMP requirements • No Legal basis for 3rd country inspection	• Auxiliary products (rescue, background) defined and label guidance (reduced) • EC has basis to inspect third countries
Safety Reporting and Risk Based Monitoring	• Safety reporting AEs, SUSARs • No Monitoring Specification	• Consolidated reporting – streamlined, DSUR • Risk based monitoring
Patient Protection and Legal Representation	• Consent (specific guidance for incapacitated adults and minors) • EU legal rep for non EU sponsors • Insurance required	• Expands info on Consent withdrawal and adds emergency consent • Co-Sponsorship, EU Contact person • National Indemnification – risk based assessment

VHP versus CTR

Voluntary Harmonisation Procedure (VHP)	Regulation No 536/2014
Single point of contact – single e-mail address VHP-CTFG@VHP-CTFG.eu	Single point of contact - single portal
National Competent Authority (NCA) collaborated assessment of the core scientific dossier	Member State (MS) collaborated assessment for Part I
Collaborated assessment coordinated by Reference National CA (REF-NCA)	Collaborated assessment coordinated by RMS
Short timeline to respond to GNAs (10 days)	Short timeline to respond to GNAs (12 days)
Possible to add new MSs - second round VHP	Possible to add new MSs
VHP decision concerns only CAs (even if some ECs participating); CA decision obtained after national phase + separate EC opinion needed in each MS	One single administrative decision per MS

In Bibliography 6

Transition to the new CT System

- Any CTA submitted at this time, is still governed by the old Directive until 3 years after go live

- A CTA ***may*** still be submitted in EudraCT and governed by the old Directive
- A CTA ***may*** be submitted in the new EU portal and be governed by the new Regulation

- All initial CTAs ***must*** be submitted in the new EU portal and be governed by the new Regulation

- **All CTAs are governed by the new Regulation,** regardless of their date of submission

In Bibliography 7

NEW REGULATION: CHALLENGES

- Recent delay to implementation – motivation and momentum loss
- Resources (Authorities, EMA, CRO/Sponsor)
- Integrating Competent Authorities and Ethics committees for joint assessment of Part I
- Harmonizing ethics committees approach to assessment across EU
- Achieving consensus across all Member States and Competent Authorities
- Agency/ Health Ministry relationships in some Member States
- Developing implementation guidance
- Research community training
- Portal
- Workload for Reporting MS

How is EU getting ready for EU Regulation

- At National and EU levels work falls broadly into three categories:
  - Development of supporting legislation
  - Process and IT systems development
  - Communications and training

- All players working for the same objective:
  - EMA
    - Portal Design/legislation
    - Working Groups/Trainings
    - Pilot Programs
  - MS/Competent Authorities
    - Legislation/Pilot Programs
  - Sponsors/CROs/SME
    - Reviewing legislation and Testing the process (applying for Pilot programs)
    - Preparing resources: training, centralised process
    - Updating SOP and WP
    - IT preparation

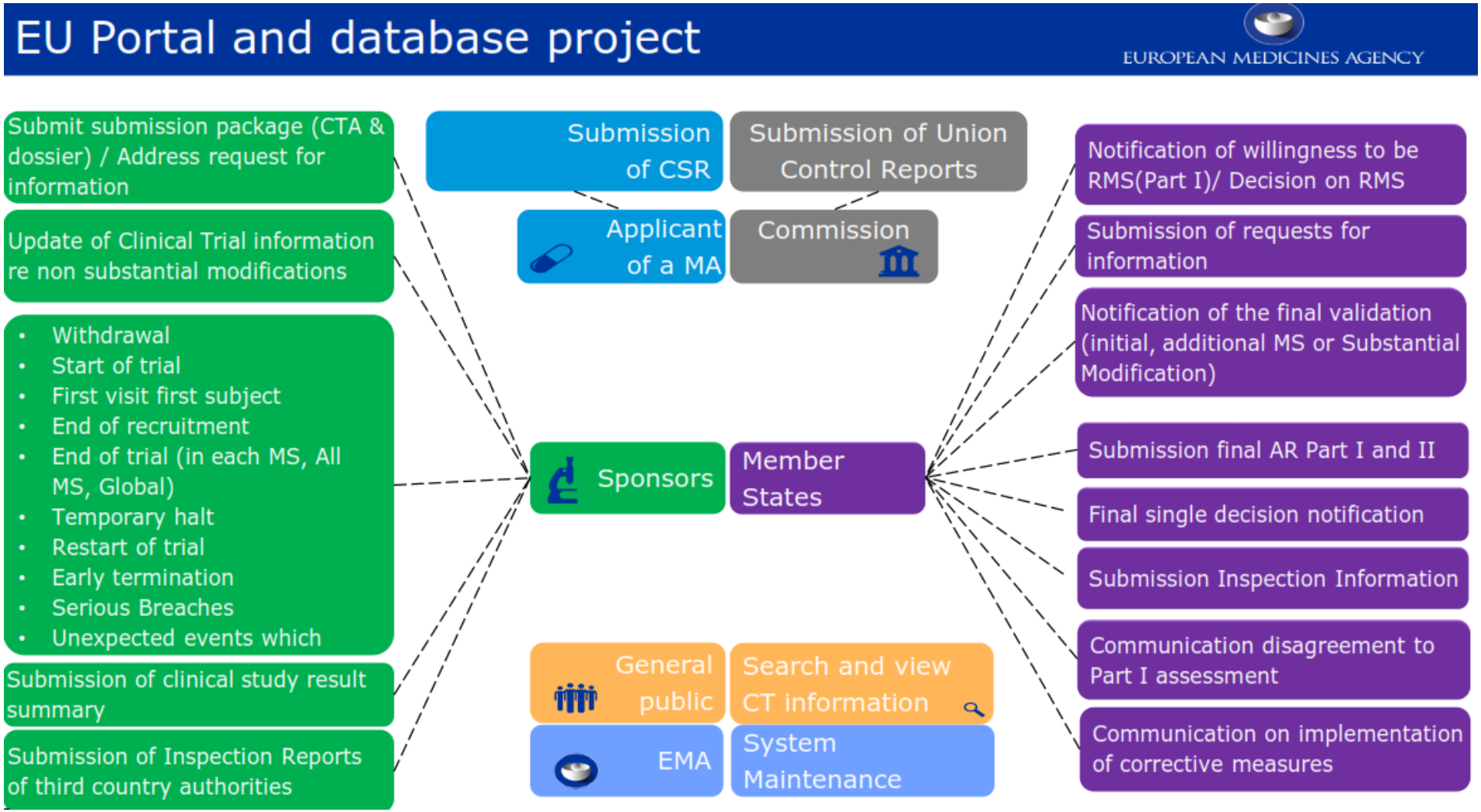
EU REGULATION: EMA

- Working on IT platforms:
  - Undergo validation and audit testing
  - Smart implementation of the EU Portal/DataBase project provides the opportunity to demonstrate Europe's commitment to clinical innovation and to encourage collaboration in advances sciences and provide early treatment opportunities for patients
  - Close partnership with sponsors during the IT development phase- to enhance the user friendliness of system from the start
  - EU portal and database project, Safety reporting project, EudraCT and EU Clinical Register Legacy project
  - Lauching UAT (User Acceptance Testing)

- Holding various stake holder meetings discussing:
  - Data Privacy/transparency,
  - Notifications, amendments and national specific updates via the electronic portal
  - Content fields for application forms

- EMA consults with the member states and stakeholders through the subgroups

EU REGULATION: EMA



In Bibliography 7

EU REGULATION: Member States

- Little Progress, major hurdles remain:
  - National IT system
  - Pilot projects
- Some progress, more actively needed:
  - Resources
- Progressing well, on target following the national implementation plan:
  - NCA-EC organization
  - EC restructure
  - Fees
  - Communication and training
  - Safety

EU REGULATION: Sponsors/CROs

- Regulatory Strategy
  - VHP/VHP plus/national/pilot programs
  - Legislative vs Experienced Approval Timelines
  - Documents availability/IP availability

1 single submission/evaluation

- Getting informed:
  - Review Regulation
  - Attend EMA stakeholder meetings
  - Feedback on EC consultation and Working Groups/organizations consultation

- CTA activities
  - Update internal documents, SOPs, WP, update communication with reg agencies policy
  - Increase communication between departments
  - Update templates: change templates (as ICF, data privacy statements, data reporting), decrease number of templates (country specific)
  - Central team to submit single application
  - Country teams prepare/compile, QC local documents for national assessment

EU REGULATION: Sponsors/CROs

- Legal
  - Legal Representative or Contact Person
  - Concept of Co-sponsorship
  - Proof of sponsor insurance to be added as a mandatory document to the initial CTA dossier

- UAT (User Acceptance Testing)
  - Volunteer to participate in testing of sponsor-related functionality of EU database and portal
  - So far, testing has included:
    - Part I application (similar to CTA)
    - Part II application (similar to ethics)
    - Addition of new Member State(s)
    - Substantial and non-substantial modifications

- Benefits:
  - Early look at new system requirements
  - Possibility to influence design and scope of portal (eg suitability for early phase studies)
  - Updates on progress of system implementation
- Drawbacks:
  - Time consuming (pre-meetings, testing, reports)
  - Difficult to fully test database & portal in allotted time (1 week)
  - Not working with 'real' clinical trial data, so testing limited

In Bibliography 9

EU REGULATION: Sponsors/CROs

- IT
  - Upgrade IT systems to be able to handle large data packages
  - Collaboration with local teams/contracted services with Publishing Group if xml required

- Resources
  - Training current resources
  - Getting new resources

- Training
  - Update whole organisation on essentials: train specific staff in new procedures
  - Specific train in use of database and portal

EU REGULATION: Training

Training content			Audience to be targeted
Module Ref	Module Title	Module Description	
CTTM01	**Introduction to the Clinical Trial Regulation**	• Overview of the Regulation • Explanation of key changes from the Directive 2001/20/EC • Overview of the transition period	• Member States • Sponsors • EMA • Public
CTTM02	**Introducing the EU Portal and Database for Public Users**	• Overview of the functionality available to Public Users • Guides on how to search and download data and the pre-defined reports on Clinical Trial information	• Public
CTTM03	**Introducing the EU Portal and Database for Registered Users**	• Overview of the core functionality available to Registered Users • Overview of the different roles which can be assigned to Users and the functionality that each of these roles provides	• Member States • Sponsors • EMA
CTTM04	**Managing Registered Users**	• Guides on how to assign a role/clinical trial access to a registered user affiliated to an organisation • Guides on how to amend/revoke the roles/CT access assigned to a user	• Administrators

In Bibliography 10

EU REGULATION: Training material

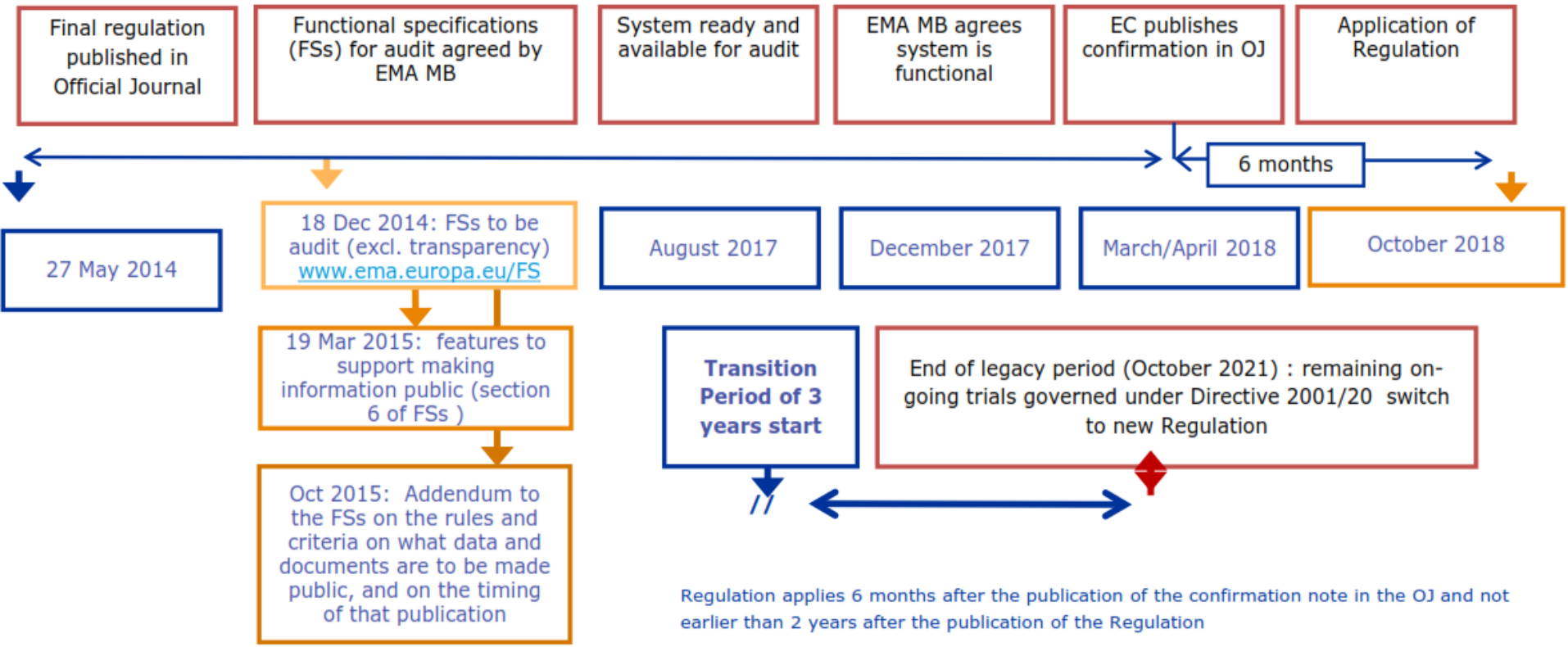
Channel	Summary of scope
• **User Manual**	• Full and comprehensive system guide – addresses happy and all alternate paths • MS Word or pdf document
• **Overview video**	• Addresses discrete functionality or topic • Level of detail varies by video type • Presented in an online MS PowerPoint presentation with voice over • Videos in similar format to UAT videos, produced using the "Snag It" tool
• **Step by step process video**	
• **Quick guide**	• Process overview • 1-2 page A4 MS Word or pdf document including screenshots of key steps. • Typically only covers the happy path
• **In-system help**	• Short "pop up" explanation of fundamental items • Templates to provide guidance on when tool tips should be provided in the system including length and purpose • Content to be derived from user manual
• **Online presentation**	• Detailed walk-through of functionality • Addresses happy path, and commonly-used alternate paths • MS PowerPoint presentation with no voice over/ video
• **Webinar**	• Interactive delivery of the material within online PowerPoint presentation • Split by stakeholder group i.e. Sponsors/ Member States
• **Face-to-face training**	

EU REGULATION: RAL role

- Regulatory strategy:
  - Be proficient in all regulatory requirements for the submission and approval of CT concerning respective geographical region (NA, LA, APA, EMEA)
  - Current options/Future option
  - Review information – drafts, EMA stakeholder meetings, regulators, UAT
- Documentation
  - Prepare current documentation aligned with the new regulation
  - Submission dossier seems similar but still a lot of detail missing
- Process for CT management
  - Communication: sponsor/Ra responsible person/Local team/centralized team
  - Document preparation, QC
- Timelines
  - Transitional period
  - Mandatory period

EU REGULATION: RAL role

"Current" Timelines



In Bibliography 7

EU REGULATION: role of the RA professional

Interaction RA - Local team - Central team

Regulatory Affairs role	Central Submission Team	Local team
• Primary point of contact for sponsor • Develop regulatory Strategy & RAPP • Communicate regulatory strategy and submission status to sponsors • Collect/compile Core Dossier Content • Ensure Senior QC of core content • Obtain EudraCT number in EU • Completion of Annex 1 in the EU • Assessment submission requirements for initial CTA and amendments • Alert local lead and central team of CTA amendments and required submissions of all types • Coordination of query responses	• QC Submission content to ensure expected submission content provided • Compile submission dossier & submit directly to regulatory agencies and CECs dossiers/RTQs • Complete local submission forms (where possible), draft cover letters • Receive queries from regulators and provide to regulatory/country leads for resolution • Enter queries into CTMS • Update CTMS, archive submission content • Deliver informational /summary translations when required • Ensure appropriate notification of receipt of queries, conditional approval, approval or rejections • Communication with regulatory authorities	• Local cover letter templates/submission templates • Contribute local perspective to regulatory submission strategy • Collect local submission content & communicate with sites • DCC of local dossier content • Completion of local submission forms (where required) local sections of Annex 1 in the EU • Official translations • Notify central submission team of local submission needs and to provide local submission content • Update CTMS • Support query resolution, final QC before reply submitted on a country level • Communication with regulatory agencies

In Bibliography 5

Contact: carla.gomes@ppdi.com

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