New European Regulation

on clinical trials, rules and implementation, where are we?

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Introduction

The first common regulatory framework on Clinical Trials (CT) in the European Union (EU) has been established in April 2001 following the adoption of the Directive 2001/20/EC (hereafter referred to as "the Directive").

The scope of the Directive covered exclusively interventional CT on Humans involving medicinal products including advanced therapy medicinal products (ATMPs). The Directive was the first attempt to a harmonisation of the requirements for CT in EU, the principles of the Directives were then transposed by each Member State (MS) under national laws.

A few years after its implementation, in December 2008, the European Commission (EC) announced the assessment of the CT Directive, that led to the release in October 2009 of a public consultation paper.

Although it was acknowledged that the directive had a positive impact on the safety, ethic and reliability of data from CT conducted in EU, the Directive presented certain limitations in particular, it did not succeed to promote clinical research in Europe as evidenced by a decreased number of CT (decrease of 25% between 2007 and 2011).

Further limitations raised included the increased cost, the lack of harmonised regulatory requirements between MS, a regulatory framework not always adapted to practical requirements and the length of procedure leading to delays in CT start.

In addition to the rules laid down in the Directive, a voluntary procedure for a harmonised evaluation of CT application (CTA) between several MSs is possible under the Voluntary Harmonised Procedure (VHP). However, this procedure can be proposed only on a voluntary basis and is not integrated into a legal basis.

Furthermore, the VHP was, at this time, restricted only to the evaluation by the National Competent Authorities (NCA). A new regulatory framework was therefore deemed necessary with the aim of restoring the competitiveness in EU for CT conduct,by simplifying and harmonising the requirements.

In February 2011, a public consultation on a concept paper on the revision of the CT Directive was issued and in July 2012 the EC adopted the proposal for a CT Regulation.

I. Clinical Trial Regulation

The Regulation EU No 536/2014 *(hereafter referred to as "the Regulation")* was adopted by the European Parliament on 16 April 2014 and entered into force on 16 June 2014. The main objectives of the Regulation are to simplify the procedures for CTA in EU with the creation of a single procedure applicable to all MS, to increase the transparency of the CT and to create an environment favourable to CT conduct in EU.

The Regulation applies to all national and multinational interventional researches on medicinal products including ATMPs.

The Regulation defines the broader concept of clinical study which includes both interventional and non-interventional studies and of clinical trial which includes only interventional studies. The Regulation introduces a new type of CT, classified as low-interventional trials, this new terminology is further explained hereafter.

The main differences between the CT Directive and the CT Regulation are summarised in Table 1 below.

Comparison of Main Features for Clinical Trials under Directive 2001/20/EC and Regulation EU No 536/2014

TOPIC	DIRECTIVE 2001/20/EC	REGULATION EU NO 536/2014
Legal basis		
	Transposition into national laws	European Regulation directly applicable
Scope		
	Interventional clinical trials One study concept: interventional clinical trials (no risk differentiation)	Interventional clinical trials. Two study concepts based on risk approach: interventional and low interventional clinical trials
Sponsorship		
	One single sponsor	Possibility for co-sponsorship
Dossier submission		
Dossier requirements	Not hamonised between MSs - one dossier per MS	One harmonised dossier for all Member State via EU portal
Dossier structure	One dossier for NCA and one dossier for EC	Part I (scientific part) and Part II (national part)
National contact(s)	Not harmonised between MSs (usually independent contact points for NCA and EC)	One single national contact point
Process	Independent submission for each MS, requires at least 2 dossier submissions for each MS (one to NCA and one to EC)	One single submission for all MSs via EU portal. Addition of new MS to the procedure, possible only after initial authorisation decision
	Sequential or parallel submission to NCA and EC	Sequential or parallel submission of Part I and Part II of the dossiers
Format	Electronic and/or paper submission	Electronic submission (EU Portal)
Entity in charge	Sponsor or principal investigator for some EC	Sponsor exclusively
Assessment		
Procedure	Independent for each MS	Part I: one single coordinated for all MSs Part II: independent for each MS
Duration (from validation to decision)	NCA: 60 days; EC: 60 days (+ 30 days for all ATMP and additional 90 days if experts consultation) Timelines not always followed in practice	60 days (+ 50 days for ATMPs)

TOPIC	DIRECTIVE 2001/20/EC	REGULATION EU NO 536/2014
Outcome		
Decision	One decision for each MS Separate decisions for NCA and EC	One single decision for each MS, includes NCA and EC decisions
Type of approval	Tacit for NCA (if no ground for non-acceptance received after the 60-day evaluation has elapsed, however national implementation can differ and certain MSs issue explicit approval) Explicit for EC	Explicit
Safety		
Reporting	No requirement to report serious breaches to protocol (however, required in certain MSs eg.UK)	7 days to report serious breaches to protocol
	SUSAR only	SUSAR and any unexpected AE with impact on benefit/risk
CT termination		
Notification	Within 90 days after trial termination	All CT-related information (protocol, assessment and decision on trial conduct, summary of trial results including a lay summary, study reports, inspections, etc.) and lay summary
Outcome		
Data published	Limited information (study design, sponsor, investigational medicine, therapeutic areas, status and results).	All CT-related information (protocol, assessment and decision on trial conduct, summary of trial results including a lay summary, study reports, inspections, etc.) and lay summary
Portal	EudraCT database	EudraCT database - EU database
Archiving		
Decision	Essential documents archived for at least 5 years	Clinical trial master archived for at least 25 years

ATMP=Advanced Therapy Medicinal Product
CT=Clinical Trial; EC=Ethics Committee
EU=European Union
MS=Member State
NCA=National Competent Authority
SUSAR=Suspected Unexpected Serious Adverse Reaction

The main changes introduced by the new Regulation are presented hereafter, however, practical guidances are awaited to understand how the new concepts will be implemented:

New legal basis

The Regulation introduces a new legal basis (replacement of a Directive by a Regulation) and implies therefore a direct applicability of the regulatory requirements between MSs without the need for a full transposition into national laws.

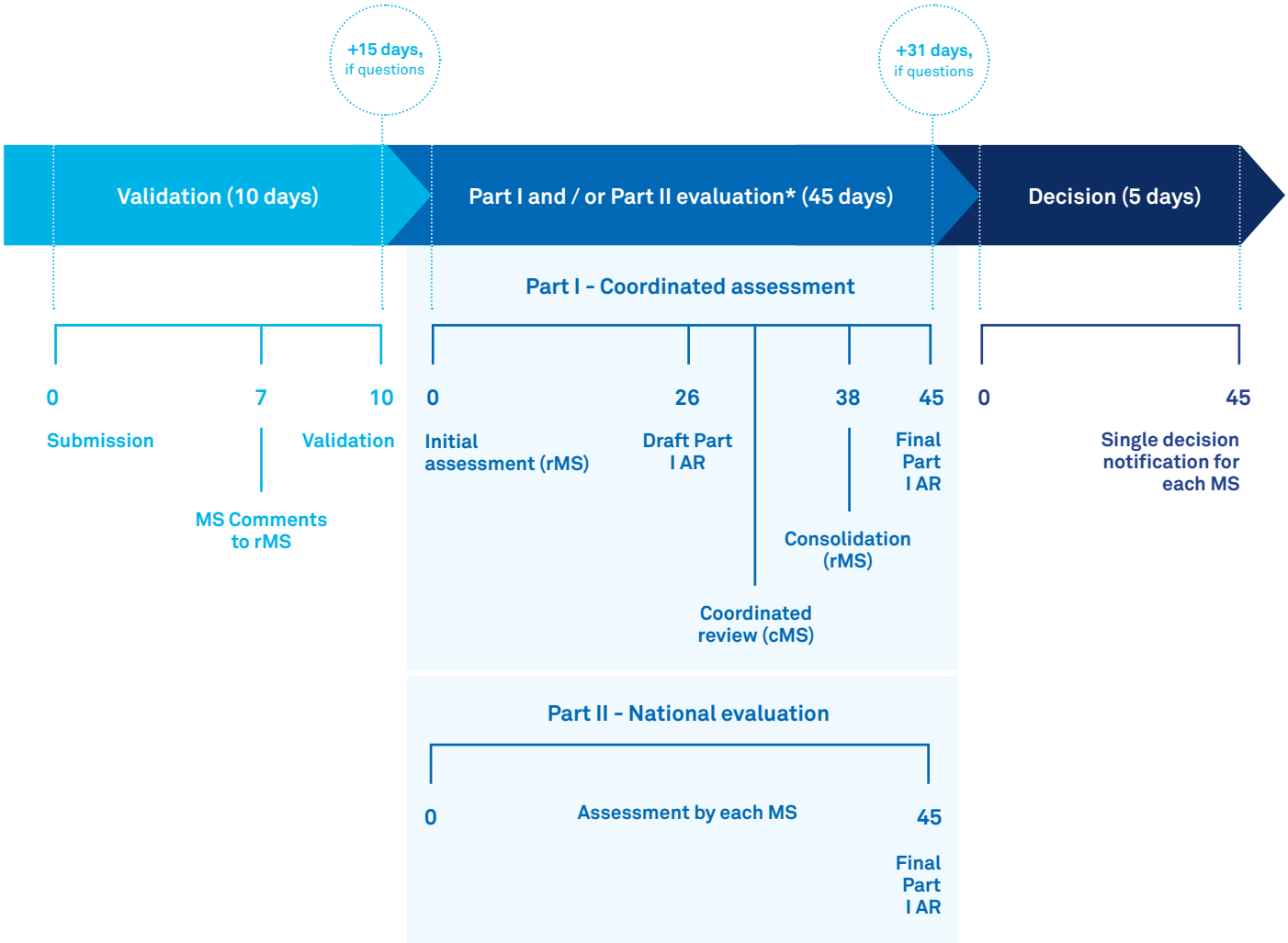
New procedure for CTA

The Regulation simplifies the process for CTA by the introduction of a common unique procedure applicable to all MSs with defined assessment timelines of 60 days including 3 phases: validation, dossier evaluation (Part I and Part II) and final decision, *(see Figure 1)*.

The CTA procedure is coordinated by a reporting MS (rMS) that is designated before the start of the procedure.

The sponsor decides on the MSs concerned (cMS) to be included in the CTA and should propose a MS to act as rMS for the procedure. If several MSs are willing to act as rMS, agreement should be reached between the MSs to designate the rMS, if no MS is willing to act as rMS, the rMS proposed by the sponsor becomes the rMS of the procedure. The submission is performed electronically via an EU portal accessible to all National Competent Authorities (NCA) and Ethics Committees (EC).

Figure 1 - Procedure for CT evaluation under Regulation EU No 536/2014



* Part I and part II evaluation can be done in parallel or sequential

AR= Assessment Report; MS: Member State

STEP	ACTION
Validation phase (10 days)	The MSs evaluate if the CTA falls into the scope of the Regulation and if the application dossier is complete. During the first 7 days, the cMS provide the rMS with their comments. After 10 days, 3 scenarii are possible: either the rMS validates, rejects the dossier or issues questions. If the application dossier is incomplete, an additional 15-day period applies as follows: - The sponsor has 10 days to acomment on the application or to complete the application - The rMS has 5 days to assess the answer of the sponsor and issue a decision on the dossier validation
Dossier evaluation (45 days)	Assessment of the dossier content starts. The dossier is composed of two distinct parts, Part I (scientific part) and Part II (national part). The evaluation of both parts is conducted either in parallel or in sequential (Part I being evaluated before Part II), a maximal period of 2 years can be applied between the evaluation of the 2 parts. In all cases, the assessment of each part lasts 45 days except for ATMP where the review period is extended to a further 50 days. **PART I** **The scientific part is a coordinated assessment where the MSs evaluate the following aspects of the application:** - Acceptability on the low-interventional nature of CT, if applicable - Benefits versus the risks for the subjects - Manufacturing and importation for the IMP - Labelling requirements - Investigator's Brochure **The assessment is conducted in 3 sequential parts:** - Initial assessment phase (26 days) where the rMS produces a Draft Part I assessment report (AR) - Coordinated review phase (12 days) where the cMS comment on the draft Part I AR produced by the rMS - Consolidation Phase (7 days) where the rMS integrates the comments of the cMS to the Draft Part I AR and produces the Final Part I AR. **An additional 31 days is possible in case questions are raised during the evaluation, according to the following calendar:** - 12 days for the sponsor to provide answers to the questions - 12 days for the MSs to evaluate the responses - 7 days for consolidation by the rMS. **The decisions regarding Part I should be the same for all MSs except if conduct of CT in the cMS result in one of the following situations:** - Participation in the CT would lead to an inferior treatment than in normal practice - Infringement of the national laws - Considerations are raised by the cMS as regards to subject safety and data reliability and robustness submitted in the application dossier. **PART II** The ethic part corresponds to a national evaluation of the following aspects of the application: - Informed consent, subject recruitment, data protection - Compensation - Suitability of investigators and of trial sites - Damage compensation - Collection/storage/use of biological samples Each MS issues a report within 45 days. As for Part I, a further 31 days can apply in case questions are raised (12 days for the sponsor to provide responses and 19 days for the cMS to evaluate the response and produce the final Part II AR).

STEP	ACTION
Decision (5 days)	Each MS has 5 days to submit a single decision (approval, approval under conditions or refusal) on the CT via the EU Portal. Of note, if a sponsor decides to withdraw the CTA during the procedure, the withdrawal is applicable to all MS.
Addition of a Member State	New MSs can only be added once the first wave of the procedure is finished i.e. when final decision is issued. The sponsor will have to submit an application dossier to the new MS through the EU portal. The rMS remains the same as for the initial evaluation procedure. The additional MSs have 52 days to give their decision to the sponsor. An additional 31-day period applies in case additional information is needed, according to the same calendar as for the initial submission.
Substantial	Substantial modifications are defined as any change to the CT made after notification of a decision likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the CT. Substantial modifications on Part I, Part II or both parts can be submitted.
	The procedure lasts 49 days and is composed of 3 phases: dossier validation, assessment and decision: - The validation phase lasts 6 days with the possibility of an additional 15-day in case of questions (10 days for the sponsor to address the questions and 5 days for the rMS to issue a decision on the validation). - The rMS has 38 days to submit the final AR to the sponsor (19 days for the initial assessment, 12 days for the coordinated review phase and 7 days for the consolidation phase). Possibility of a 31 days clock stop. -Each MS submits its decision within 5 days. The timelines for substantial modification for Part II are the same.

Introduction of a new type of CT, the low-interventional trials

Low-Interventional CT are defined in Article 2 (3) of the Regulation as CT where the investigational medicinal products (IMP) (excluding placebos) are authorised.

The use of the IMP in the low-interventional trial protocol is in accordance with the terms of the marketing authorisation (MA); or the use of the IMP is evidenced -based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the MSs concerned.

Finally, the additional diagnostic or monitoring procedures (eg. weighing, blood withdrawal through a pre-existing catheter, analysis of saliva etc.) defined in the trial protocol do not raise more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any MSs concerned.

Low-intervention CT correspond to categories A and B of the Organisation for Economic Cooperation and Development (OECD) which introduces different risk categories for CT.

The low-intervention CT are subject to the same application procedure as any other CT, with adapted dossier requirements. The cover letter shall indicate if the clinical trial is considered by the sponsor to be a low-intervention clinical trial and shall contain a detailed justification thereof.

Less stringent rules apply with regards to monitoring *(Article 48 of the Regulation)*, requirements for the content of the master file *(Article 57 of the Regulation)*, traceability of the IMP *(Article 51 of the Regulation)* or damage compensation *(Article 56 of the Regulation)*.

Introduction of risk proportionate approaches in clinical trial

The Regulation introduces a new concept of risk proportionate approach to apply less stringent rules to trials conducted with medicinal products already approved and which pose only minimal risk compared to normal clinical practice. Risk adaptation applies mainly to low-intervention CT but can also apply to any CT, if dully justified.

A public consultation took place from 1 June 2016 to 31 August 2016 on «Risk proportionate approaches in clinical trials».

Risk in CT should be considered at the system level (eg. facilities, SOP, etc.) as well as the trial level (eg. IMP, trial design, etc.). A risk based quality management for CT should include the following steps: risk identification, risk evaluation, risk control, risk review, risk communication and risk reporting.

Risk adaptation can be applied to the following areas; however, the risk assessment and mitigation plan should include justifications for the level of adaptation proposed:

- Safety reporting *(Article 41 of the Regulation)* with selective recording and reporting of adverse events (AEs) and adaptations to expedited reporting from the investigator to the sponsor for certain serious events. This applies in particular to already marketed products.

- IMP management *(Article 51 of the Regulation)* with adapted provisions for traceability of IMP. This applies in particular to already marketed products that could be sourced from normal stock of the community or hospital pharmacy.

- Trial management with adapted provisions for trial monitoring *(Article 48 of the Regulation)* where the sponsor should determine the extent and nature of monitoring on the basis of an assessment (eg. methodology and objective of the CT, how intervention deviates from normal clinical practice, etc.)

- Trial documentation with adapted content of the Trial Master File *(Article 57 of the Regulation)* by combining documents (eg. job descriptions and résumés) or by absence of documents as a result of implementation of other risk proportionate measures.

Up to now, no recommendations have been issued to describe how risk based approach will be presented in the CTA dossier.

New features on informed consent: simplified means in cluster trials and specific conditions for emergency trials

The general rules for the protection of subjects and informed consent are unchanged from the principles laid down in Directive 2001/20/EC. The Regulation introduces the possibility for obtaining informed consent by simplified means in case of cluster trials and defined specific conditions in emergency situations:

- Simplified means in cluster trials

(Article 30 of the Regulation)

When a CT is conducted in a single MS, informed consent can be obtained by simplified means (i.e. no written consent required) if the simplified means are not contradictory with national laws, if the CT is low-interventional where the IMPs are given in accordance with the terms of the MA, if the methodology of the CT requires that groups rather than individual subjects receive different IMPs in a CT, if there are no interventions other than the standard treatment of the subjects concerned and if the protocol provides information on how information will be given to the subjects and justifies the reasons for obtaining consent by simplified means.

Overall, it remains the MS responsibility to implement or not the simplified means in cluster trials and differences across the MSs are expected and already observed. Indeed, among the 2 countries (Belgium, Spain) having started to implement the Regulation into national law, Belgium rejected this principle while Spain incorporated it (see Part III.a).

In order to apply for a CTA with informed consent under simplified means in cluster trials, the cover letter shall indicate if the methodology of the clinical trial requires that groups of subjects rather than individual subjects are allocated to receive different investigational medicinal products in a clinical trial, and as a consequence whether informed consent will be obtained by simplified means.

- Specific conditions in emergency situations

(Article 35 of the Regulation)

Emergency situations relate to cases where for example a patient has suffered a sudden life-threatening medical condition due to multiple traumas, strokes or heart attacks, necessitating immediate medical intervention. In case CTs are conducted in emergency situations, informed consent may be obtained and the information on the CT given after the decision to include the subject is taken.

If, following the intervention, the subject (or his/her legally designated representative) does not give consent, the subject should be informed of the right to object to the use of data obtained from the CT.

New possibility for co-sponsorship

(Article 72 of the Regulation)

The CT Regulation introduces the possibility for co-sponsorship (several sponsors) of CT according to the rules laid down hereafter. In case of co-sponsorship, all sponsors are either subject to all responsibilities of a sponsor, or respective responsibilities for each sponsor are defined by written contracts.

The Regulation foresees that each of the following responsibilities are undertaken by one of the sponsors:

- being a contact point for receiving questions from subjects, investigators or MSs and answering them
- implementing the measures (termination, suspension or modification) requested by MS.

Derogation to the obligation for a legal representative of the sponsor in the Union

(Article 74 of the Regulation)

As currently applicable under the Directive, if the sponsor of a CT is not established in the Union, the sponsor must ensure that a natural or legal person is established in the Union as its legal representative.

The Regulation introduces the possibility to derogate to the need for a legal representative; in this situation, a contact person in the Union for all communications with the Sponsor will be sufficient.

Each MS will have the possibility to accept or reject the possibility to derogate to the need for a legal representative.

Safety reporting requirements

(Chapter VII of the Regulation)

New requirements in terms of safety reporting are included in the Regulation. As such, any unexpected AE with an impact on the benefit risk assessment should be reported in the database within 15 days.

In addition, any serious breach to the study protocol should be reported within 7 days.

The EMA shall set up an electronic database as a module of the Eudravigilance database to streamline and harmonise the submission process of SUSAR Suspected unexpected Serious Adverse Reactions) and annual safety reports (Article 40 of the Regulation).

MSs will collaborate to evaluate the DSUR (Development Safety Update Report). In addition, a standard web-based structured for the reporting of SUSAR will be developed.

Increased transparency *(Article 81 of the Regulation)*

The EU database publicly available should include all CT-related information generated during the life cycle of a CT i.e. the study protocol and decision on trial conduct, a summary of the results including a lay summary, study reports, inspections, etc.

The publication of CT-related information is applicable to all CT unless confidentiality is justified under certain grounds such as personal data or commercially confidential information protection.

It is therefore expected, that Phase 1 studies would remain excluded from the transparency requirements. However, Guidance from the EC on this aspect would be helpful to clarify the situation.

II. Implementation steps

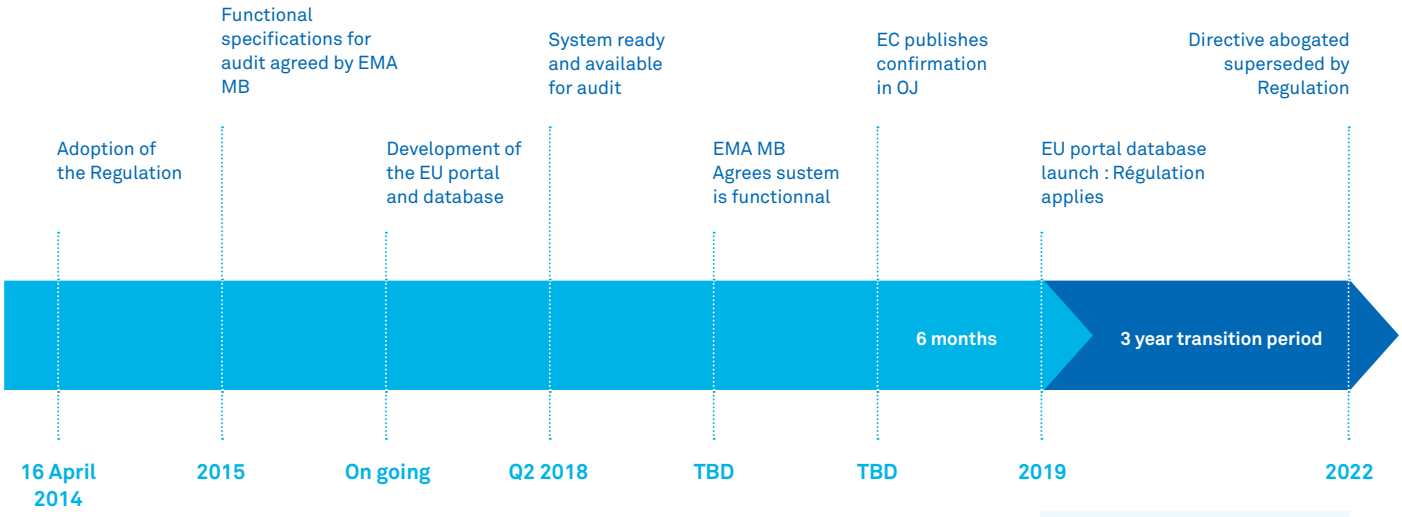
As per the Regulation, milestones have been defined before the Regulation becomes applicable that takes into account the development of an EU Portal and Database as presented in Figure 2.

After the publication and adoption of the Regulation in 2014, the EMA committed to develop the EU portal and database. During 2015, the Management Board (MB) of the EMA agreed on the functional specifications to be audited.

The EU portal and database developments are still ongoing. The audit is planned for Q2 2018. After completion of the audit, the EMA MB will declare the system functional. Publication by the EC of the confirmed functionality in the Official Journal will launch a 6-month clock stop after what the Regulation will come into application.

An implementation period of 3 years for the new Regulation will be started according to the following milestones (Figure 2):

Figure 2: EMA Key milestones and timelines for the launch of Regulation EU No 536/2014 (as of December 2017)



3 year transition period :

1st year : CTA submitted under Directive or Regulation

2nd and 3rd year : submission under Regulation but trials authorized under the Directive remain under it.

EMA=European Medicines Agency
MB: Management Board
OJ: Official Journal of the EU
TBD=To Be Determined
Q=Quarter

- First year: applications for CT are possible either under the Directive or the Regulation.
- Second and third year: applications for CT must be performed under the Regulation and ongoing CT started under the Directive remain under the Directive principles.

At the end of the implementation period, the Regulation will become fully applicable for all CT and the Directive abrogated.

According to the information available in December 2017, the CT Regulation is planned to become applicable in the second half of Q2 2019, after what the transition period will start.

III. National Implementation by Member States

In order to get prepared to the new Regulation, MSs adopt different strategies. Certain countries including Austria, Belgium, France or Germany have initiated pilot phases while other countries such as Spain or Belgium have already translated into national regulations the principles laid down in the Regulation.

A review and comparison of the implementation steps undertaken by these MSs are presented hereafter.

A. Pilot phases

France and Germany initiated pilot phases in 2015 followed by Austria in 2016, and more recently by Belgium and Sweden in 2017. The purposes of the pilot phases are to develop processes and procedures for the joint assessment of CTA by NCA and EC under the rules of the Regulation.

The pilot phases are conducted under the rules of the Regulation without prejudice of the Directive 2001/20/CE, which is currently the applicable legal basis.

Each country undertakes the pilot phase under its own rules, a comparison of the differences between the different countries proposing Pilot Phases is presented hereafter.

Scope of CTA eligible to the pilot scheme differs between countries

The scope of CTA eligible to the pilot scheme differs between countries: all initial CTAs are eligible to the Pilot phase in France while more restriction is applied for the eligibility in other countries such as Belgium where applicants can submit a voluntary request that will then be assessed on a case-by-case basis by the Federal Agency for Medicine and Health Products (FAMHP).

In Germany, an extension of the scope of the pilot phase is planned over the time: at the start of the pilot, only initial CTA will be included, the scope will evolve to include also later substantial modifications of CTA evaluated under the pilot scheme.

Timelines of the pilot phase

In the context of the pilot phase, timelines adjustments are needed to mimic the calendar of the Regulation (60-day procedure excluding additional time in case of questions) and to remain compliant with the timelines for CTA procedures applicable under the current Directive 2001/20/CE (60-day procedure with no additional time in case of questions).

The timelines for CTA evaluation under the pilot scheme in France are of 36 days in absence of questions (7 days for the validation, 26 days for the dossier evaluation and 3 days for the decision), an additional 24-day period applies when questions are issued (12 days for the sponsor to submit responses and 12 days for the NCA and/or EC to review the responses), so that the total duration of the procedure does not exceed 60 days.

In Belgium, the CTA procedure lasts 38 days in absence of questions, in accordance with the currently applicable national law. The timelines are defined as follows: 10 days for validation, 23 days for assessment and 5 days for the decision.

An additional maximal period of 27 days applies in case of questions raised during validation (10 days for responses and 5 days for review of responses) or during assessment (12 days for responses).

Transposition in national laws

Differences are also observed with regards to the bodies involved in the assessment of Part I, where only the NCA is involved in France (at the exception of the trial methodology that is now assessed by EC as per the applicable National law) while, in Germany or Belgium, both EC and NCA assess this part of the dossier.

Assessment and CTA process

The submission process is centralised to a single a national point in Belgium while parallel and simultaneous submission to the both NCA and EC is still required in France and Germany. Of note, the application must be submitted in Germany to the competent EC but also to the concerned local EC.

Differences between countries are also noticed in terms of coordination of CT evaluation under the pilot phase: in Belgium, an independent college was created to be the main contact point with the AFMPS for the EC in Belgium and to assign CT to EC while in France, there is currently no centralisation of contact points for the EC, each EC being assigned by random draw.

Outcome of pilot phase after 2 years of implementation in France

As one of the objective of the pilot phases is to anticipate and get prepared on the new process for evaluation of CTA under the Regulation, reports on the experience acquired by the MSs are of interest. As of now, France only has made publicly available reports. A review of the latest report issued in October 2017 (period covered by the report from September 2015 to September 2017) published after 2 years of implementation is provided hereafter.

A total of 260 projects were submitted that represented 14.2% of applications received by the French National Agency (ANSM) for CTA. A total of 50 dossiers were not considered acceptable mainly because of validation issues or because EC could not manage them. Sponsors submitting applications were either industrials or academics and concerned trials were mainly Phase 3 (about half of the trials) and to a lesser extent Phase 2 (26.7%), Phase 1 (19.0%) or Phase 4 (6.7%) studies. A total of 210 applications had been received and outcome on the procedure was available in 193 cases at the time of the report.

A review of the finalised procedures indicates that an authorisation was granted by the ANSM and a positive opinion given by the EC for 65.8% (127/193) of the dossiers, the average duration for evaluation was of 68.9 days.

Overall, the main difficulties identified pertained to the prolonged duration of the procedure. Discussions are ongoing and actions planned to reduce the timelines for dossier assessment and become compliant when the Regulation will become applicable.

B. Transposition into national legislation

Belgium and Spain have started to transpose into national laws the principles of the Regulation.

Belgium

In Belgium, the new law on CT Regulation has been published under the Belgisch Staatsblad/Moniteur Belge on the 7th of May 2017. The national law indicates the positioning of Belgium on the organisation within the MS to coordinate the CTA procedure under the Regulation and on the non-mandatory aspects of the Regulation, as follows:

- The nomination of a national contact point being the National Competent Authority (AFMPS) and the creation of an independent College as the contact point with the AFMPS for the EC in Belgium. The College is responsible to assign CTA to EC.
- The non-implementation of the simplified means in case of cluster trials (defined in Article 30 of the Regulation)
- The evaluation procedure for mononational phase I Trials remains of 20 days

Spain

Even though no pilot phase has been initiated, the principles of the Regulation have been transposed in Spain by the Royal Decree 1090/2015 that entered into force in January 2016. The Decree agrees with most of the principles of the Regulation subject to national implementation such as informed consent by simplified means.

Among the measures taken, the Spanish Agency of Medicines and Medical Devices (AEMPS) is designed as the national contact point and had to write a “collaboration memo” to establish the responsibilities between the AEMPS and the EC for Investigation with medicinal products (CEIm). The AEMPS is also responsible to establish a way to communicate and exchange information with the CEIm, and to create a registry of clinical studies with medicinal products for human use on its website.

As reported by Jimenez et al, 2017 , a “collaboration memo” was published in February 2016 and clarifies the roles and responsibilities during the assessment procedure:

- Part I will be evaluated by the AEMPS and the CEIm, while Part II will only be assessed by the CEIm.

- The AEMPS will write the AR of phase I clinical trials and of clinical trials including ATMPs or allergens. The CEIm will prepare the draft report for all other trials. Phase IV trials and low-intervention trials will only be assessed by the CEIm.

- As a general rule, the quality, preclinical, pharmacology, and toxicology data will be evaluated by the AEMPS. With regards to clinical data, the AEMPS will assess aspects pertaining to statistics, GCP compliance, the presence of a Data Safety Monitoring Committee, and the definition of the end of trial.

- The classification of low-intervention trial will be assessed by the CEIm and all other aspects not covered by the AEMPS. The first assessment report will result from the collaboration of the AEMPS and the CEIm.

- In terms of dossier requirements, it will be possible to submit all documents corresponding to Part I in English at the exception of the authorisation form (both in English and Spanish) and of the protocol summary and the labelling to be submitted in Spanish only. With regards to Part II, for any documentation intended to the patient should be submitted in Spanish.

IV. Conclusion

Three years after the release of the new Regulation on CT, progress has been made at the EU and MS levels to get prepared when the Regulation comes into force. Even if the Regulation corresponds to a more stringent new legal basis than the current one (Directive), the new requirements remain sufficiently broad so that flexibility is still given to the MS to implement them (eg. assessment of Part I of the dossier by both NCA and EC or exclusively by NCA, flexibility to nominate national contact point, etc.). Overall, sponsors should benefit from the new Regulation through a simplification of the submission process (single electronic submission) and well-defined evaluation timelines.

As the Regulation will deeply impact the requirements for clinical trials in Europe, it is important for the EMA, MSs and sponsors to get prepared:

- In addition to the development of the EU portal and database, the EMA publishes Guidelines to inform sponsors and MSs on the new terminologies introduce by the Regulation, as such the following documents were released “Risk proportionate approaches in clinical trial” or “Summary of Clinical Trial Results for Laypersons” or “Ethical Considerations for Clinical Trials on Medicinal products conducted with Minors”.
- Pilot phases launched by a few MSs have stimulated interest to sponsors and allow to gain experience on both sides. Feedback available on the pilot phases has shown that the main challenge for compliance to the Regulation, will be to perform the evaluation within the defined timelines.

- Thorough regulatory survey is necessary to remain up to date on the progress of the implementation phases at EU level (eg. follow-up on progress of EU portal development, etc.) but also at the individual MS level (eg. transposition into national laws, etc.).

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