



The CTR from a QP's Perspective

CTS Europe 2025 Barcelona

Dr. Andreas Schwinn, Feb 2025

The CTR from a QP's perspective



01	Introduction	<ul style="list-style-type: none">• History• New terminology
02	Expectations	<ul style="list-style-type: none">• Centralized Application• Consistent Approval Procedure• One Set of Documents
03	Transition, CTD to CTR	<ul style="list-style-type: none">• WORKLOAD• Consolidation or Harmonization prior to transition
04	Challenges	<ul style="list-style-type: none">• Initial Difficulties• Cross-referencing to CTD trials not allowed• Inconsistent application of the same rules, e.g. QP declaration• Multiple versions of part I documents possible
05	Positive Surprises	<ul style="list-style-type: none">• Consistent Approval Timelines• Single Set of Documents• Label is a part I document
06	Labeling	<ul style="list-style-type: none">• Story of a mistake: Period of use on the immediate packaging• CTR Labeling requirements
07	Supply Strategy impact	<ul style="list-style-type: none">• Supply strategy for comparators and AxMPs• Submission per Active Substance and ATC code
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Introduction

History of the Clinical Trial Regulation (EU) No 536/2014

16 April 2014	CTR version date
27 May 2014	Published in the Official Journal of the European Union
28 May 2016	Entry into force
	CTR Art 82 instructed EMA to draw up specifications for an <i>EU portal and EU database</i> on Clinical Trials, verify its meeting the functional specifications in an independent audit, and, publish a note in the OJEU when successful
31 Jan 2022	CTR became applicable, new CTAs can be made under CTR in the CTIS (Clinical Trial Information System)
31 Jan 2023	New CTAs must be submitted under CTR
31 Jan 2025	All Clinical Trials running under CTD needed to be transitioned into CTR

Introduction

New terminology

- Clinical trial vs. clinical study (= non-interventional)
- Reporting member state (RMS)
- Member state concerned (MSC)
- Substantial modification (SM)
- Non-substantial modification (NSM)
- Article 81.9 NSM
- Application to add a new MSC
- Request for information (RFI)
- Mother trial + daughter trial
- Urgent safety measure (USM)
- ...

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Our Expectations to the CTR ...

- A consistent ruleset on Clinical Trials across the EU.
- An environment that is favorable for conducting Clinical Trials.
- Streamlined applications via a
 - Single entry point or EU portal, a
 - Centralized Database, with
- One single set of documents, assessed in
 - One harmonized review and authorization procedure.
- Better transparency of clinical trials and trial outcomes through public access to the database.

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Transition

All trials needed to be transitioned from CTD to CTR

- Transition was a huge effort
 - 150 internal Roche studies
 - The last transitioning application was approved mid January ✓
 - IITs and collaborations - approximately the same number
 - We have transitioned fewer studies than expected ?
- The Expedited Administrative Procedure helped a lot to facilitate the transition
 - Simplified dossier requirements 🚀
 - Speedy approval timelines (22 days) 🚀
 - In case of RFIs => normal timelines



Transition

- After 31 Jan 2025, all Clinical Trials
Not transitioned to CTR must stop
 - → No release of trial medication
 - No recruitment and dosing is allowed
 - Certain post-treatment activities are possible



Transition

- Problem: Transition requires consistent part I information for all MSCs, requiring:
 - Resolution 1:
Consolidation prior to transition with Substantial Amendment under CTD
 - Impact on timeline
 - Possibility of rejection
 - Resolution 2:
Harmonized Documentation with transitioning application
 - presenting core information and local differences


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Challenges

Initial Difficulties

- What documents do I get out of CTIS?
 - Approval Screenshot
 - Conditions
 - Assessment Report Part I
- How do I get those documents?
 - Internal process 
 - IITs (Investigator Initiated Trials) ?
- Also the authorities experienced challenges



Challenges

Cross-referencing to CTD trials is not allowed

- Cross-referencing to an IMPD in an other trial can only be done to a CTR trial (It is called mother and daughter trial);
 - CR was the primary mechanism for IITs.
 - It allows a Sponsor to perform a trial with a product from other manufacturers.
 - No IMPD needed to be exchanged;
- No new IITs and collaboration products were initiated for about 18 months !
- Then, the IMPDQ-only submission was introduced
 - An IMPD is submitted by the manufacturer under a separate EU CT number
 - It requires additional logistics
 - But, it solves the problem ✓
- Transitioning of trials with cross-references to CTD studies was not allowed, either
 - Resolution: Finally, it was allowed for the transitioning application ✓

Challenges

Inconsistent requirements for QP declarations

No QP Declarations are required (per CTR Q&A)

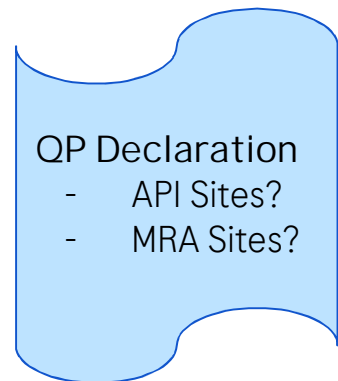
- for Active Pharmaceutical Ingredient sites
- for MRA Sites

Single MSCs requested QP declarations that are not required [?]

e.g. for

- 3rd country Biologics Drug Substance manufacturers
- A Cell Bank Manufacturer

We urge the authorities to align and adhere to their own guidance!



Challenges

Transparency Requirements - QP Declaration

New request in 2022:

- Provide redacted QP declarations, without name and signature ?
- Together with the signed QP version.

Rationale:

- QP declarations were published in the EU database
- QP declarations contain the QPs name and signature
- Publishing personal information is against data protection rules / the CTIS transparency rules

Sharing an unauthorized document is a GMP violation

Luckily, the revised CTIS transparency rules removed the QP declaration from the list of published documents ✓

Challenges

Multiple sets of cmc Data are still possible !

In contrast to the “One Set of Documents” paradigm:

- CTR Q&A states, "... each Member State Concerned takes an individual decision and can disagree with a positive conclusion by the RMS. ... several versions of the part I documents may exist"
 - ➔ Multiple sets of cmc Data are still possible
- At Roche, we only observed different study protocol versions in the same trial, e.g., one study arm was not approved in a certain member state.
 - ➔ This is release-relevant, since we should not release the respective product for this country.
- Also different IMPD versions could be possible
- Do we have to return to a country-specific approach for regulatory compliance ?

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Positive Surprises

Consistent approval timelines  

- Default approval timeline: 60 - 106 days
(depending on validation questions and RFI)
- Expedited administrative procedure for transitions: 22 days
(in case of RFIs, default applies)
- Addition of a new MSC: 52-83 days
- Mono-national trials significantly shorter approval timelines defined nationally

Conclusions:

- For most countries, this is longer than before
- HAs still struggle to consistently meet those timelines
- Ethics approval is already included



Positive Surprises

Single Set of Documents 

- We indeed have a single set of documents
- Under CTD we had on average 7 sets of documents (7 EU countries per study)
- All substantial modifications are approved at the same time

However, there are exceptions to the rule => see challenges ...




Positive Surprises


Visibility of conditions, RFIs, and Commitments 

- Conditions are specified on the Conclusion Page, together with the Approval Information per country
- Conditions are written in English - not local language as with CTD
- The assessment reports identifies Requests for Information (RFIs) from the Health Authorities
- All RFI + Responses are clearly visible to the QP
- Sponsor responses would provide evidence of any commitments that might be release relevant.

Positive Surprises

Label is element of part I documentation 

- The label is an element of the part I documentation
- All labels will be submitted in all countries
- All labels are “approved” with the respective application

➔ For the first time, I as a QP, have undoubted evidence of the approved label - for all Member States Concerned 

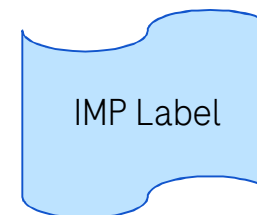
2024-512383-65-00 [Excerpt from: Assessment Report Part I, Quality](#)

3.8 Labelling

Are the proposed labelling in line with ANNEX VI of the Regulation Yes ☒ No ☐ NA ☐

Assessor's comment:

Note



Submitted



Approved

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Labeling

Period of use on the immediate packaging - the long story of a mistake

The finally published version of Annex VI states:

Section A.1.

1. The following particulars shall appear on the immediate and the outer packaging:

...

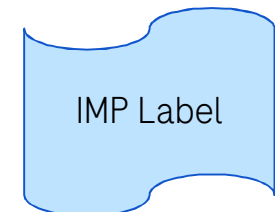
(k) period of use (expiry date or re-test date as applicable), in month and year format ...

➔ This was in contrast to

- the “old” Annex 13
- the concept of relabeling for use-date-extensions

➔ Industry had kicked off huge projects to comply with this requirement ...

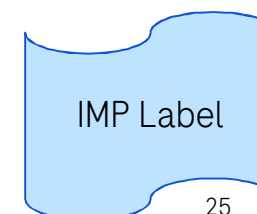
Annex VI was revised on 06 Sep 2022 to remove this requirement



Labeling

New labeling requirements

- Member states may allow foreign language labeling, e.g. English, for IMPs administered by a physician or qualified healthcare professional
- Commercial products in Clinical Trials may be used without any labeling
- Note: Minimal labeling proposed for comparators
 - Main contact
 - Clinical trial reference
(allowing identification of the clinical site, investigator, sponsor, and subject)
 - For clinical trial use only
- Re-labeling/re-packaging can be done in hospitals
 - For use in the same country and trial
 - Without MIA and certification



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Supply Strategy - Comparators and AxMPs

Relabeling in hospitals

Re-labeling/re-packaging can be done in hospitals

- For use in the same country and trial
- Without MIA and certification

My concerns are:

- A lack of supply chain control,
- Higher costs for local sourcing,
- Potential for misuse of medication outside the intended Clinical Trial,
- Difficulties in performing drug accountability,
- And the potential to negatively affect the reliability of study data.



Supply Strategy - Comparators and AxMPs

Submission per Active Substance or ATC code

- Commercial products can be submitted "per active substance or ATC code"
- This allows changing between different Generic Products with different Marketing Authorization Numbers without a submission.
- Supply shortages of generic products are frequent - a seamless replacement of an unavailable product could be very beneficial.

Excerpt of an Application Form

2023-507093-40-00	SUBSTANTIAL MODIFICATION	SM-1 - Part I	26/09/2024 8:01
Role: Auxiliary Name: FLUTICASONE PROPIONATE			
Product: Multiple EU MP number			
Active substance description			
EU Medicinal Product number/medicinal product unique ID:			
Multiple EU MP number			
Is this a specific paediatric formulation:			
No			
Strength:			
500µg			
Medicinal product name:			
FLUTICASONE PROPIONATE			
Product authorisation status:			
Authorised			
Pharmaceutical Form:			
INHALATION POWDER			
Medicinal product other name:			
Inhaled corticosteroid			
Sponsors product code:			
Medicinal product role in trial:			
Auxiliary			

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Conclusion

- The CTR is the most significant regulatory development for Clinical Trials since a long time
- Regarding IMPs since the first Annex 13 in 1996
- Dealing with it was/is a learning experience

- Version 6.8 of the CTR Q&A was my trigger to dig deeper ...
- I found that people are interested in what I concluded of my studies
- This led me to create this presentation and share it with you
- I hope you enjoyed the experience

- What may be right for me might not be right for you
- Let us share our different views, try to understand and learn ...

Other Noteworthy Facts ...

Please refer to the article

CTR Implementation - A QP's Perspective **GMP Journal**

Andreas Schwinn
11.07.2024

<https://www.gmp-journal.com/current-articles/details/ctr-implementation-a-qps-perspective.html>



Thanks a lot for your attention!

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Doing now what patients need next