EC-DG SANTE/HMA-CTFG/EMA joint training on the Clinical Trials Regulation (EU) 536/2014 - Changes to trials (submission and classification)

Lene Grejs Petersen, Senior Adviser, Clinical Trials

9-10 MARCH 2021

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Submission of Substantial Modifications (SM)

Submission of SM

- Submission of the first SM in case of an Art 5 or Art 11 application
- Submission of consecutive SMs
- Submission of part I/II SMs in case of ongoing Art 14 assessment
- Submission of part II SM in case of ongoing part II SM in a different MS
- Submission of multiple SMs by the same sponsor to several trials with the same IMP

Strict and complicated rules

The CTR introduces a high-level of coordination between the MSC for the authorisation of substantial modifications in a clinical trial with the aim to:

– create an agile, robust and predictable assessment process with increased scrutiny through the joint review and harmonised assessment.

Process for submitting SM

In order to support the assessment and authorisation of substantial modifications during the life-cycle of the trial following its approval, the following basic principles had been agreed for the submission of subsequent substantial modifications.

This process ensures:

- compliance with the Regulation,
- the stability of trial documentation for the entire time of the assessment for all assessors and
- the validity of ongoing assessments and decisions in all Member States concerned.

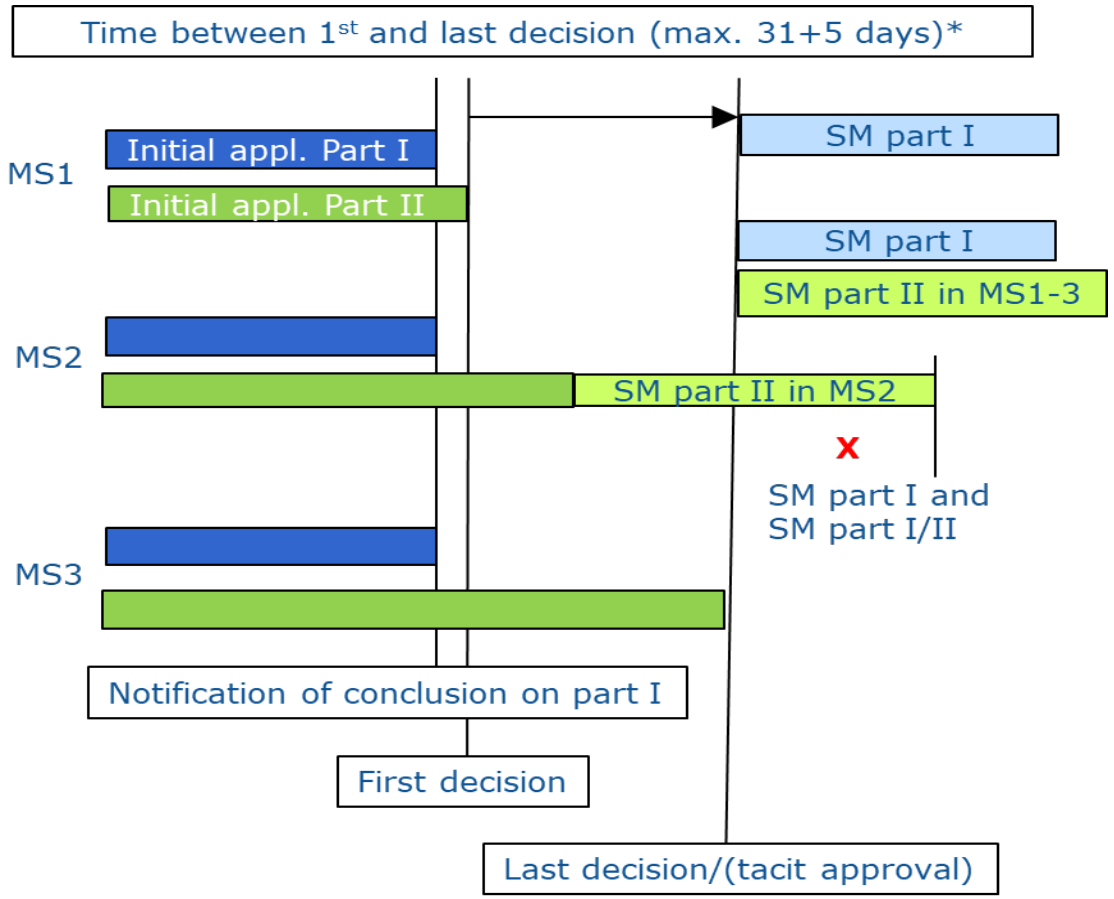
The submission of the first substantial modification application following an initial application under Art 5 or Art 11 of the CTR

- the first substantial modification can be submitted only after the **decision of all MSC which received the initial application is notified or made by tacit approval under Art 8.6. and at least one of them authorised the trial**

- the last Member State notifying its decision (or authorised the trial by tacit approval) determines when a part I or part I+II SM can be submitted.

- Time between 1st and last decision (max 31 + 5 days)
- maximum time difference between first and last decision/tacit approval in case the “fastest” MSC notifies a decision without RFI either to part I or part II of the application, while the “slowest” takes maximum time for the assessment (including a part II RFI) of part II of the dossier

Submission of first SM following an initial full application under Art 5



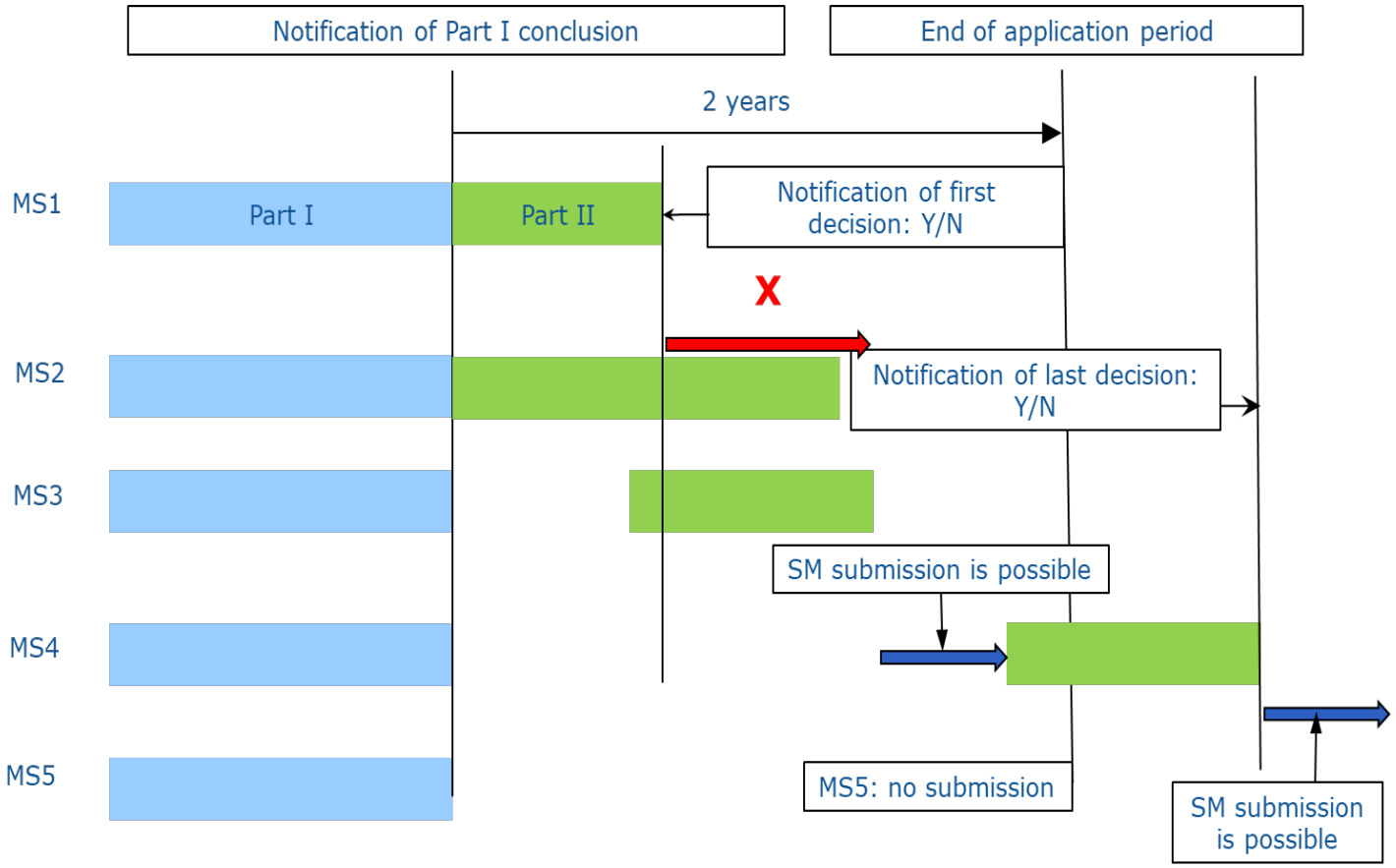
LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

SM after an application under art. 11

- a part I or part I&II SM can be submitted only after the decision on the complete application is notified by all MSCs, which received the full application and at least one MS authorised the trial
- All MSCs, which received part I of the initial application would participate in the harmonised assessment of the part I SMs, independently if they received part II as well or not

- Submission of an SM part I or part I/II is not possible if there is an ongoing (part I or part II) assessment in any of the MSC. When all MSC which received part II of the initial application dossier notified its decision (and there is at least one authorisation or approved the trial through tacit approval), a part I/part I+II SM can be submitted. Part II SMs can be submitted in those MS, which authorised the trial even when there is an ongoing assessment of part II of the initial application in a different MSC

Submission of first SM following an initial full application under Art 11



LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

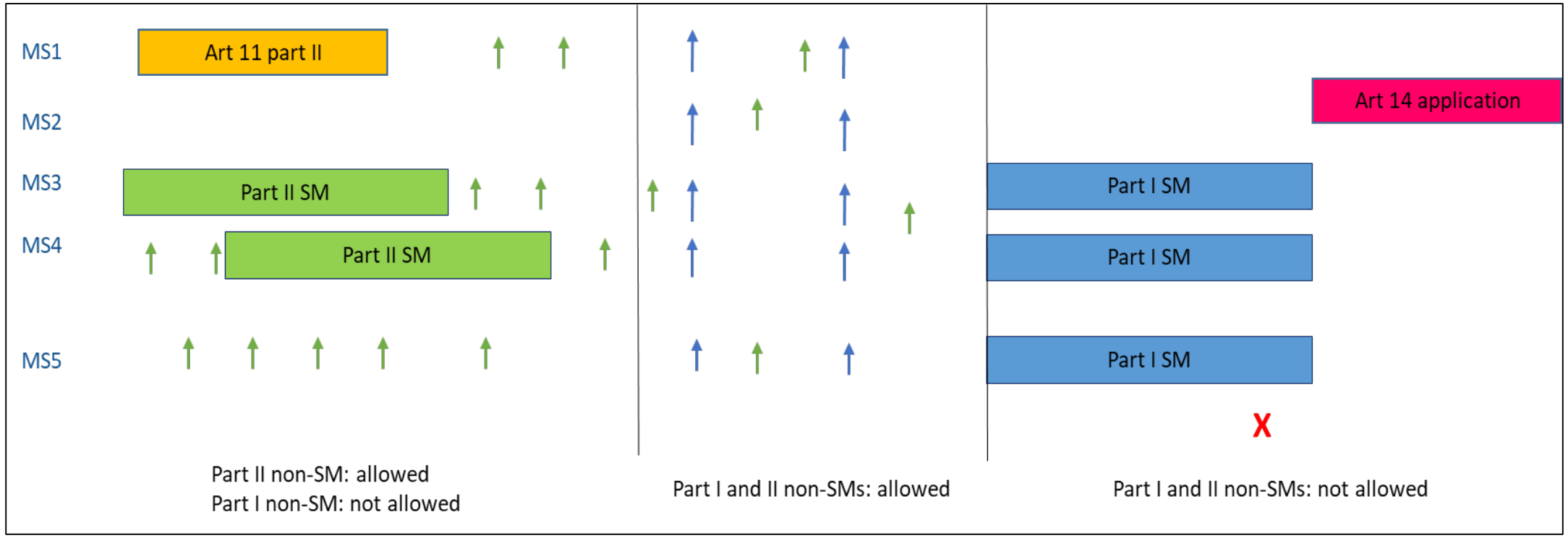
Overview of changes allowed following an initial application under Art 5, Art 11 or Art 14

		Are these changes allowed when another activity[1] is still ongoing?				
		Part I only substantial mod application	Part II only substantial mod application	Part I & Part II substantial mod application	Submission of application for an additional member state	Update of the database with relevant changes that are not substantial modifications (art. 81.9)2
Ongoing activity[1]	Initial application (art. 8)	No	No	No	No	No
	Initial application (art 11)	Yes, when all MSC, which received full application notified its decision with at least one authorisation /authorised the trial by tacit approval	Yes, in those MSC which already authorised initial application, if there is no ongoing SM assessment in this country (meaning that the decision on an SM has been notified)	Yes, when all MSC, which received full application notified its decision/authorised the trial by tacit approval with at least one authorisation	Yes, when all MSC, which received full application notified its decision/authorised the trial by tacit approval with at least one authorization and there is no ongoing part I or part I/II SM assessment	- Part I: when there is no ongoing assessment of initial application or part I/partI+II or partII SM - part II: in those MSC which authorised the trial if there is no SM assessment in this country
	Addition of (a) member state(s) concerned (art. 14, see Q&A 2.3)	No	part II SM can not be submitted in the additional MCS assessing the initial art 14 application (part II SM submission is possible in those MSC which authorised the trial if there is no ongoing SM assessment in them)	No	Only to MS that is not an MSC or evaluating an assessment to become an MSC	No

The submission of consecutive substantial modification application following an initial application under Art 5 or Art 11 of the CTR

- Submission of a part I or part I/II SM is always possible if there is no ongoing part I, part I/II or part II SM assessment in any of the MSCs; meaning that all MSCs issued a decision on a previous SM application or authorised it through tacit approval (the “slowest” MS drives the process).
- Part II SM application can be submitted if there is an ongoing part II SM assessment in a different MSC. Part II non-SM (Art 81.9) can be updated in CTIS in one MSC even when there is a part II SM assessment ongoing in a different MSC

Consecutive SM



– Green arrows: Part II non-SM, Blue arrows: Part I non-SM

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

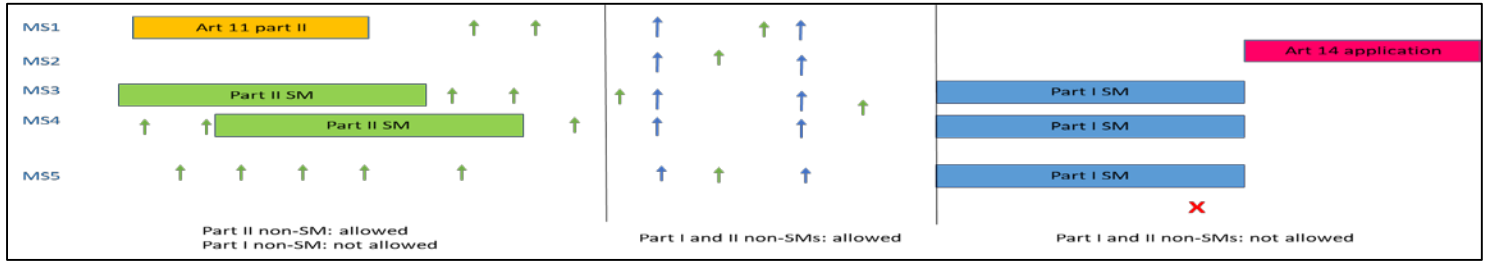
Overview of changes allowed following trial authorisation under Art 5, Art 11 or Art 14

– (see details in Q&A 2.3)

		Are these changes allowed when another activity[1] is still ongoing?				
		Part I only substantial mod application	Part II only substantial mod application	Part I & Part II substantial mod application	Submission of application for an additional member state (Art 14)	Update of the database with relevant changes that are not substantial modifications (art. 81.9)2
Ongoing activity[1]	Part I only substantial mod application (art. 19)	No	No	No	No	No
	Part II only substantial mod application (art. 20)	No	Yes, in those MSC, which authorised the trial if there is no ongoing Part II SM assessment in them	No	Yes	Yes, in those MSC where there is no ongoing part II SM assessment
	Part I & Part II substantial mod application (art. 23)	No	No	No	No	No

Submission of part I/II SMs in case of ongoing Art 14 assessment

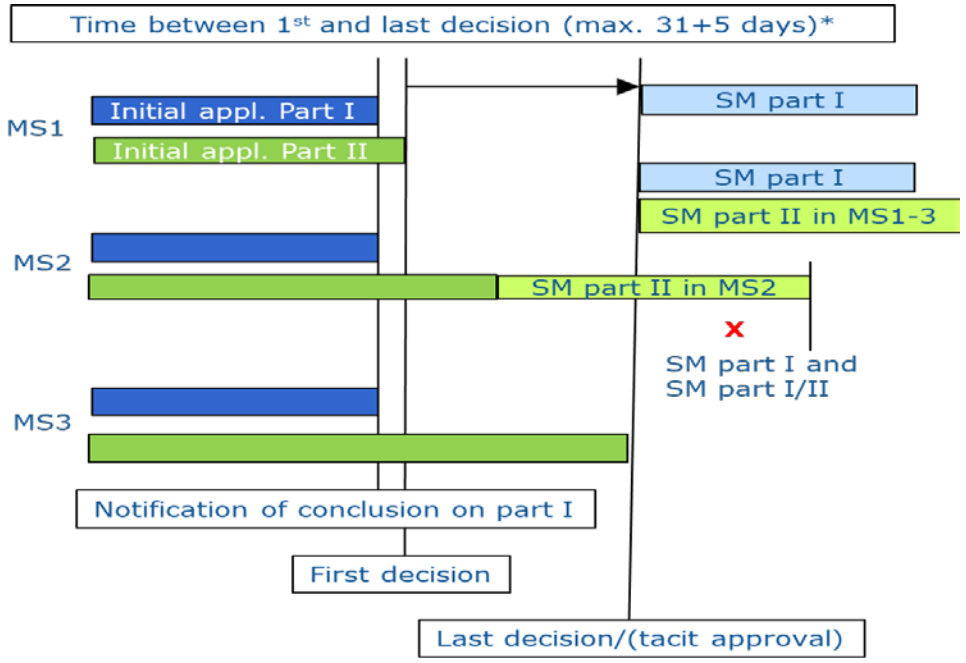
- Article 14 application for an additional member state concerned can be submitted in an Art 11 process if there is no ongoing assessment of initial or part I and part I/II SM in any of the MSC.
- In this case, part I or part I/II SM application can not be submitted until there is no decision notified on the Art 14 application. Part II SMs can be submitted in those MSC where there is no ongoing assessment.
- And vice versa: Submission of a part I or part I/II SM is not possible when there is an ongoing Art 14 assessment (as it might have part I implications), part II SM can be submitted in a different MSC than the additional MSC

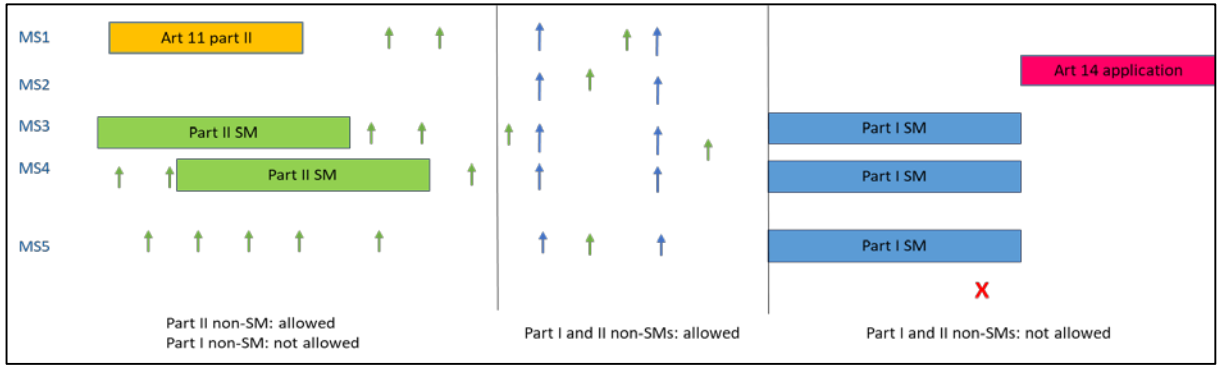


LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Submission of part II SM in case of ongoing part II SM in a different MS

– Part II SM application can be submitted if there is an ongoing part II SM assessment in a different MSC.





LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Submission of multiple SMs by the same sponsor to several trials with the same IMP

- In cases of substantial modifications (SM) related to the investigational medicinal product dossier (IMPD) (Quality, safety or efficacy), to the investigator's brochure (IB), reference safety information or any other common document used in multiple clinical trials it is recommended to submit these modifications for authorization as a single request for all clinical trials of the same sponsor and IMP
- The cover letter shall list all the clinical trials to which the application for the SM applies together with the EU trial numbers (see additional requirements in Annex II, slide from Stefan Strasser) and their responsible RMS.

Go home message

The CTR introduces a high-level of coordination between the MSC for the authorisation of substantial modifications in a clinical trial with the aim to:

– create an agile, robust and predictable assessment process with increased scrutiny through the joint review and harmonised assessment.

This process ensures:

– compliance with the Regulation,

– the stability of trial documentation for the entire time of the assessment for all assessors and

– the validity of ongoing assessments and decisions in all Member States concerned.

Questions?

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY