Conference
"EU Clinical
Trial Regulation"

EU Clinical Trial Regulation – A view from the Industry

Judith Creba, Executive Director,
EU Regulatory Strategy, Novartis Pharma AG
University of Basel, Law Faculty
16 December 2016

NOVARTIS

Disclaimer

This presentation represents the thoughts and opinions of the presenter and does not necessarily reflect those of Novartis and its affiliated companies.

This presentation may contain strategies/concepts/projects which may be aspirational in nature and may need significant modifications before implementation. Novartis will only implement programs that are fully consistent with all applicable laws and regulations as well as Novartis policies.

NOVARTIS

Agenda

- Introduction
- Key areas of procedural changes
- External activities
- How to prepare for implementation?
- Key priorities and expectations in implementation
- Conclusion

NOVARTIS

The EU Clinical Trial Regulation (536/2014) provides new rules for conduct of clinical trials in the EU

- Aims of the new regulation
  - Reduce unnecessary administrative burden without compromising subject safety, quality
  - Increase the attractiveness of the EU for clinical trials
- Replaces current clinical trial directive with a more harmonised approach
  - Change from a directive to a regulation represents a more stringent legislative approach to ensure better harmonisation
  - Single EU CTA dossier filed through a new EU Portal and database
  - Pan European approach leading to a single decision from each member state (MS) covering both scientific and ethical parts completed in same overall timelines
- Implementation depends on the availability of the new EU Portal and database - **October 2018 at the latest**
- Covers all interventional trials as currently
- Major impact on clinical trial operations in companies

NOVARTIS

CTReg Summary - Key Aspects

Application date: earliest 2 years after publication
- Transitional rules
- Linked to functionality of EU Database

Regulation
- Binding in its entirety
- Directly applicable in all MSs by all stakeholders
- Report after 5 years

Scope
- Interventional, national and multinational clinical trials with medicinal products in EU independently of sponsor (industry, non-commercial, academics)

Role of COM
- Controls (incl. outside EU)
- Support MS coordination (CTAG Committee secretariat)
- Delegated acts to update provisions in the Annexes on application dossier, safety reporting, labelling & GMP

Role of EMA
- Set- up and maintain EU database & portal
- Coordinate inspections

Single submission dossier
One format/ content (Annex I/ II)

EU portal/database by EMA
- For all communication: Sponsor – MS & between MS

Assessment
- Part I (general dossier): joint by reporting MS and concerned MS
- Part II (national dossier): national by reporting MS and concerned MS
- MS to organise the assessment process by authorities and ethics committees consistent with Regulation

One single decision via EU portal
- By each concerned MS on Part I & II
- Defined opt-out mechanisms for MS from joint Part I assessment

Assessment Times
- Validation: 10 days (+15 days clockstop)
- Assessment: 45 days (+ 31 days clockstop)
- Decision: 5 days
- Optional to seek advice for ATMPs and biological products: 50 days

Transparency Provisions
- Summary of results to be published within 1 year of end of trial
- CSR to be submitted to database 30 days after grant of MA for the MP

Informed Consent
- Strengthened provisions
- Maintenance of specific existing national provisions

Safety Provisions
- Streamlined provisions;
- Sponsor direct reporting into EurdraVigilance

Not included:
- EU decision for clinical trials
- Separate system for purely national CTs
- Imposed language regime for submission
- Regime for non-commercial trials

Key areas of procedural change

NOVARTIS

Key procedural differences with the new Regulation

Current Directive	New Regulation
Multiple dossiers for Health Authorities (HA) and Ethics Committees (EC) in each MS	Single submission (HA+EC) to the EU portal and database
Multiple scientific assessments	Single scientific assessment coordinated by a reporting MS
Multiple ethical reviews performed	Each MS to provide single ethical review
Variable timelines for HA and EC	Same timelines for HA/EC in all MSs (60-106 days)
Multiple decisions by each MS	Single decision per MS (HA+EC), tacit approval provision enforces timelines
Variable timelines for amendments	Harmonised timelines and coordinated review for modifications (49-95d)
Addition of countries by separate application for each MS (variable)	Integrated process for addition of countries within defined timelines (52-83d)

Key areas of change

Dossier/documentation

- 1 single dossier for all EU countries involved in trial:
- Part I (HA part)
- Part II (National EC)

Submission/application process

- Submit to new EU Portal and database
- Submit Part I and II together (alternative strategies possible)
- Substantial modifications (amendments) possible but sequentially

Assessment and decision

- Part I (coordinated) and Part II (national) assessment in parallel
- Regulated timelines (e.g.12 days to answer questions)
- Single decision on Part I/II at same time by each and all countries

Single dossier content

Part I	Part II
Cover letter EU Application form Protocol Investigator brochure GMP documentation for IMP IMP Dossier AMP dossier Scientific Advice and PIP Labelling of IMP	***Documentation per member state*** Recruitment arrangements Subject information, informed consent and consent procedure Suitability of investigator Suitability of facilities Proof of insurance cover Financial and other arrangements Proof of payment of fee

NOVARTIS

External activities

NOVARTIS

On-going external implementation

Many aspects to be clarified and developed

EU Commission

- Delegated and Implementing Acts – GMP and GCP
- Chairing ad hoc group for MS on implementation

EMA

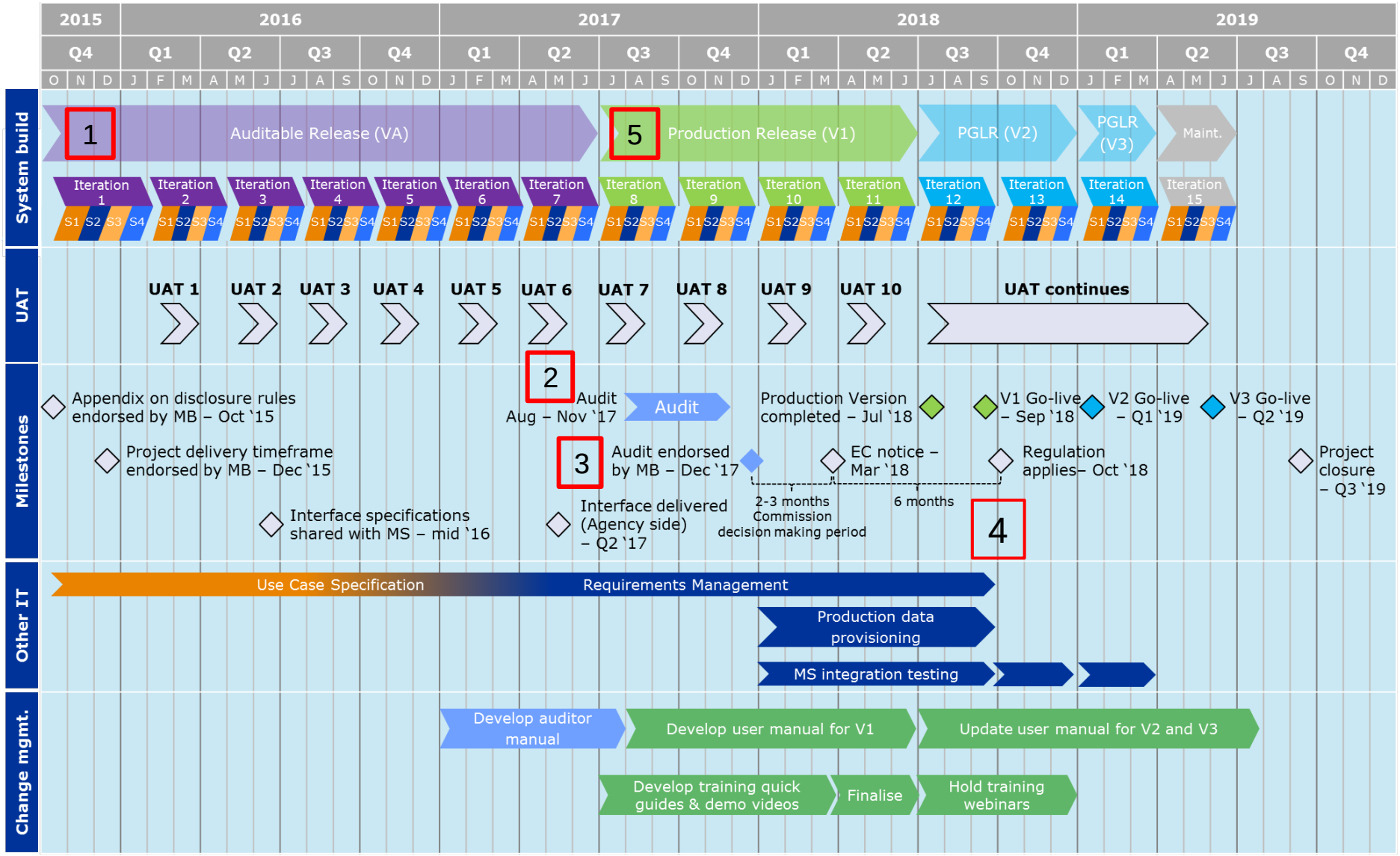
- Set up of the EU Database/EU Portal
  - Collaboration with Stakeholders
- Guidelines

Member State Level

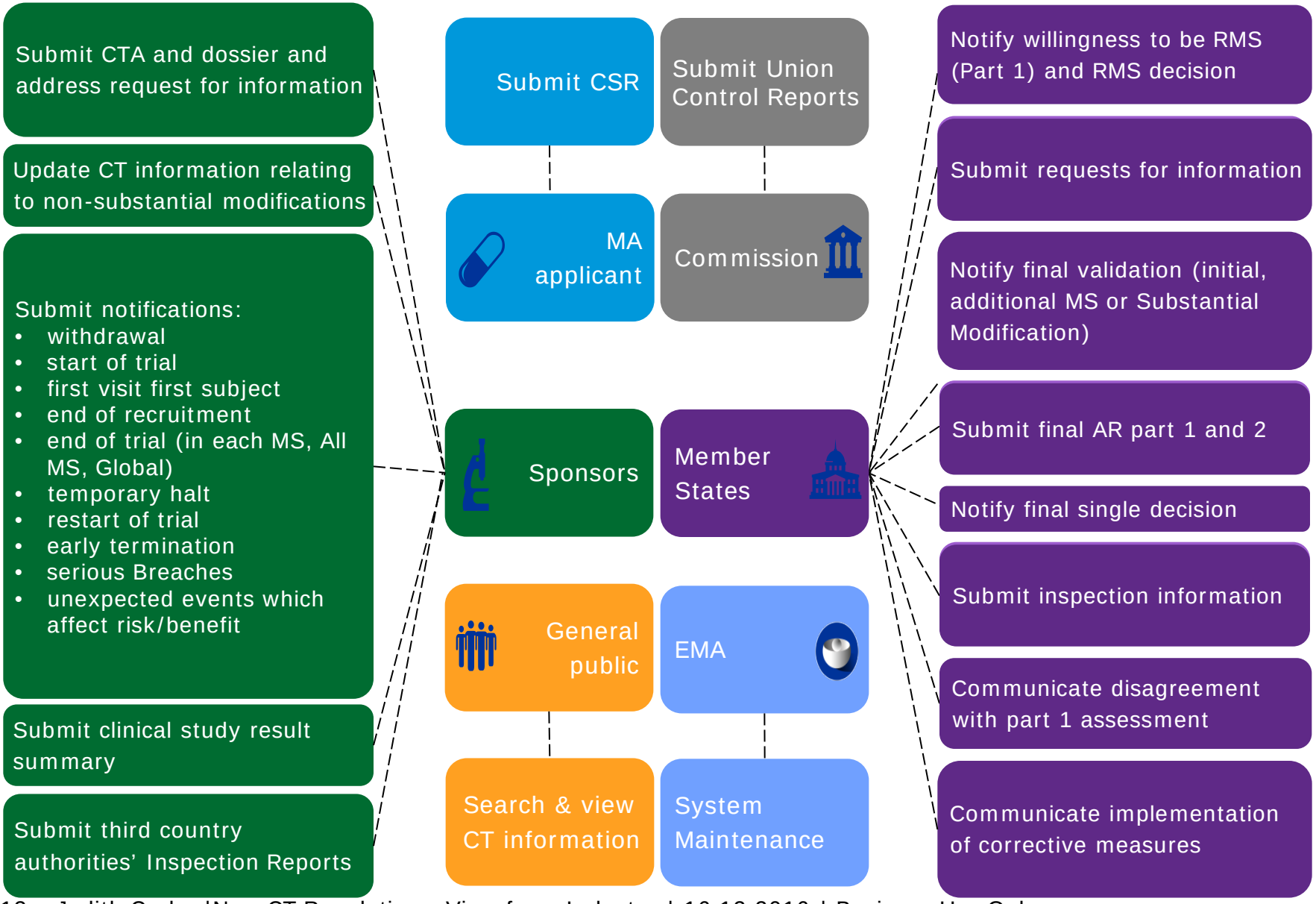
- Organisation & collaboration between HA and Ethics Committees
  - National pilots e.g. France, Germany
- Link with EU Portal and database
- Fees, waivers, penalties for infringements, appeal process
- Transposition of regulation into national law

EU portal and database - Maximum project timeline

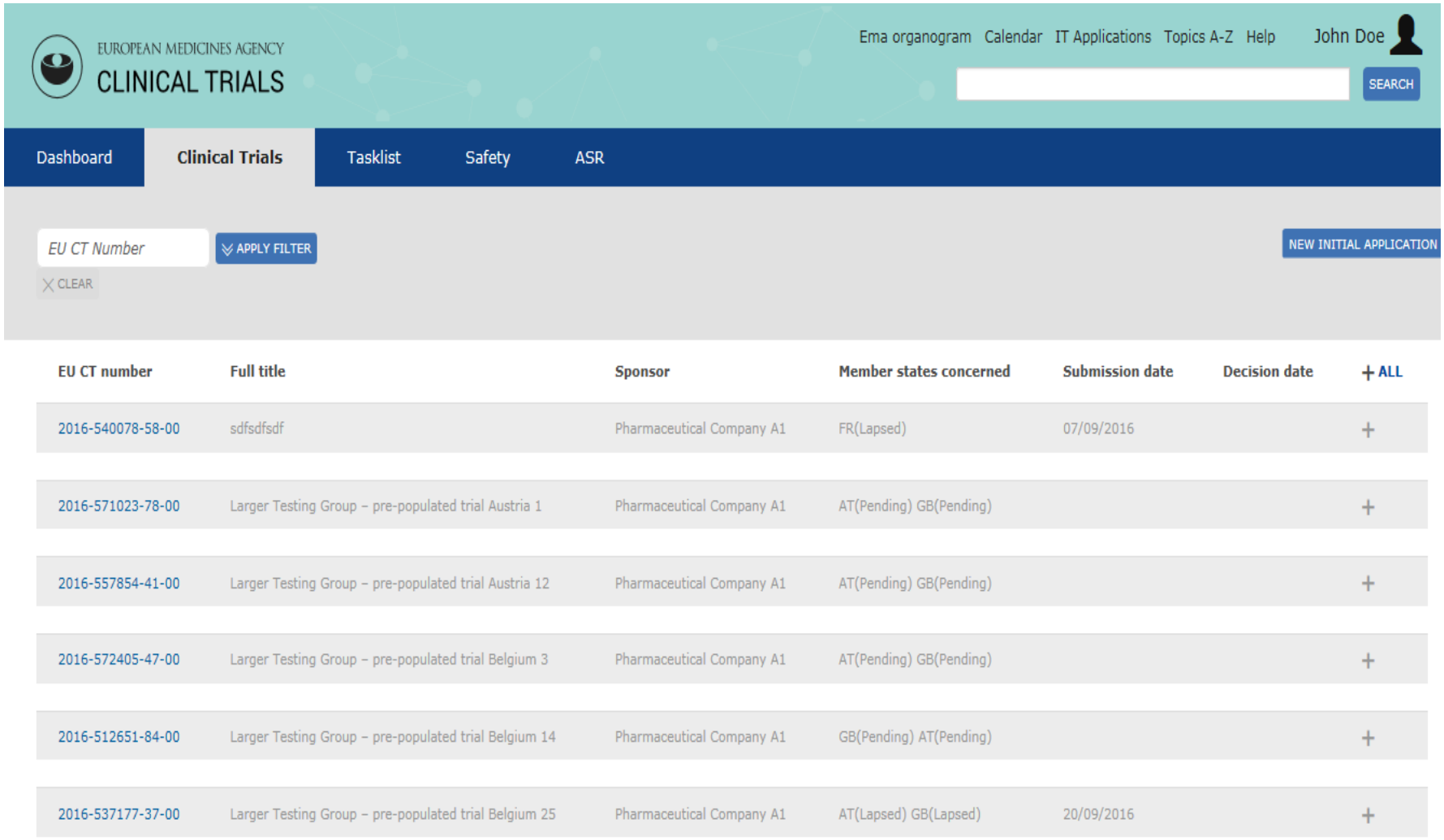
EUROPEAN MEDICINES AGENCY



EU portal and database – system activities



View of EU Portal and database as seen in user testing

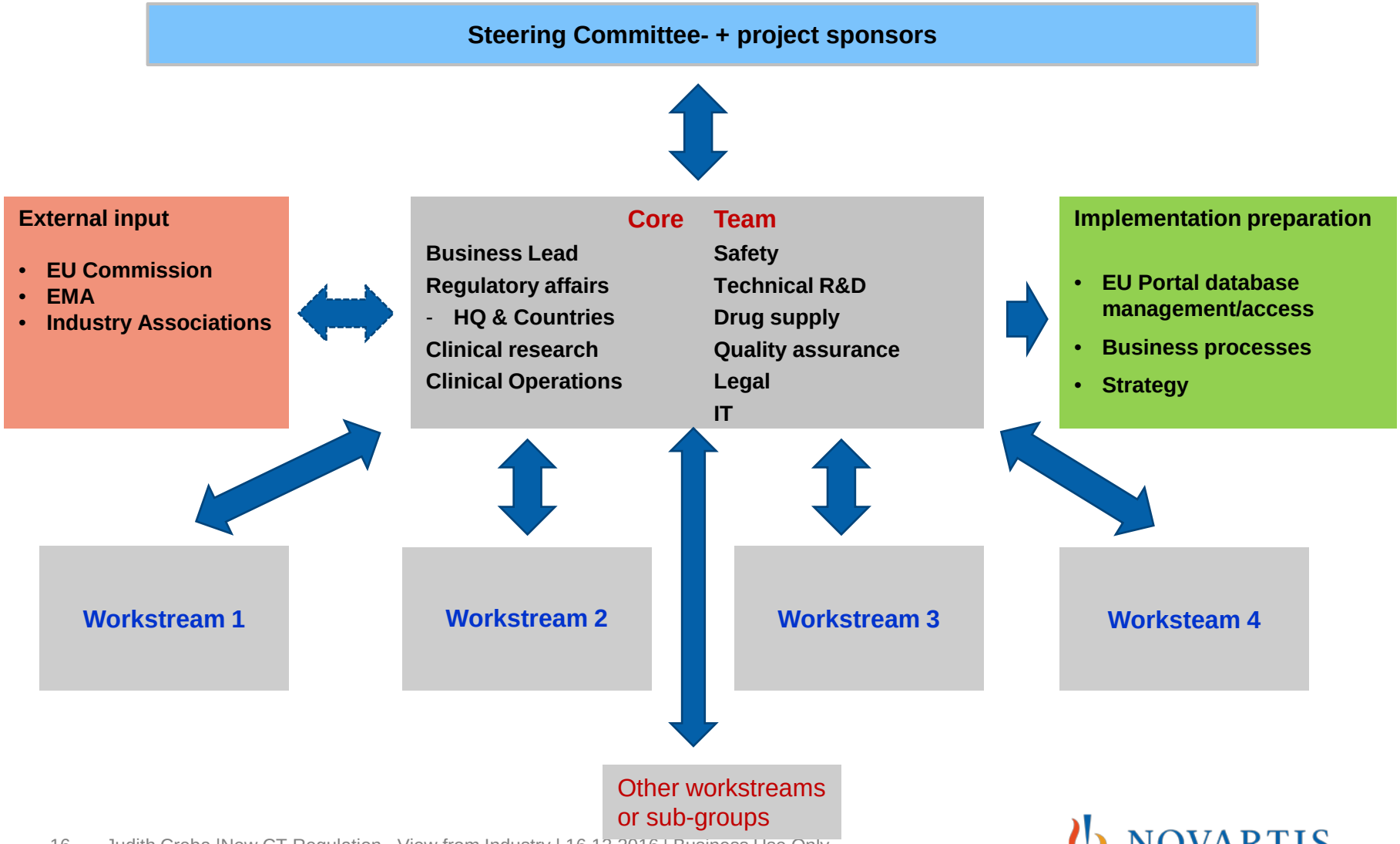


NOVARTIS

How to prepare for implementation?

NOVARTIS

Internal cross-functional project team structure

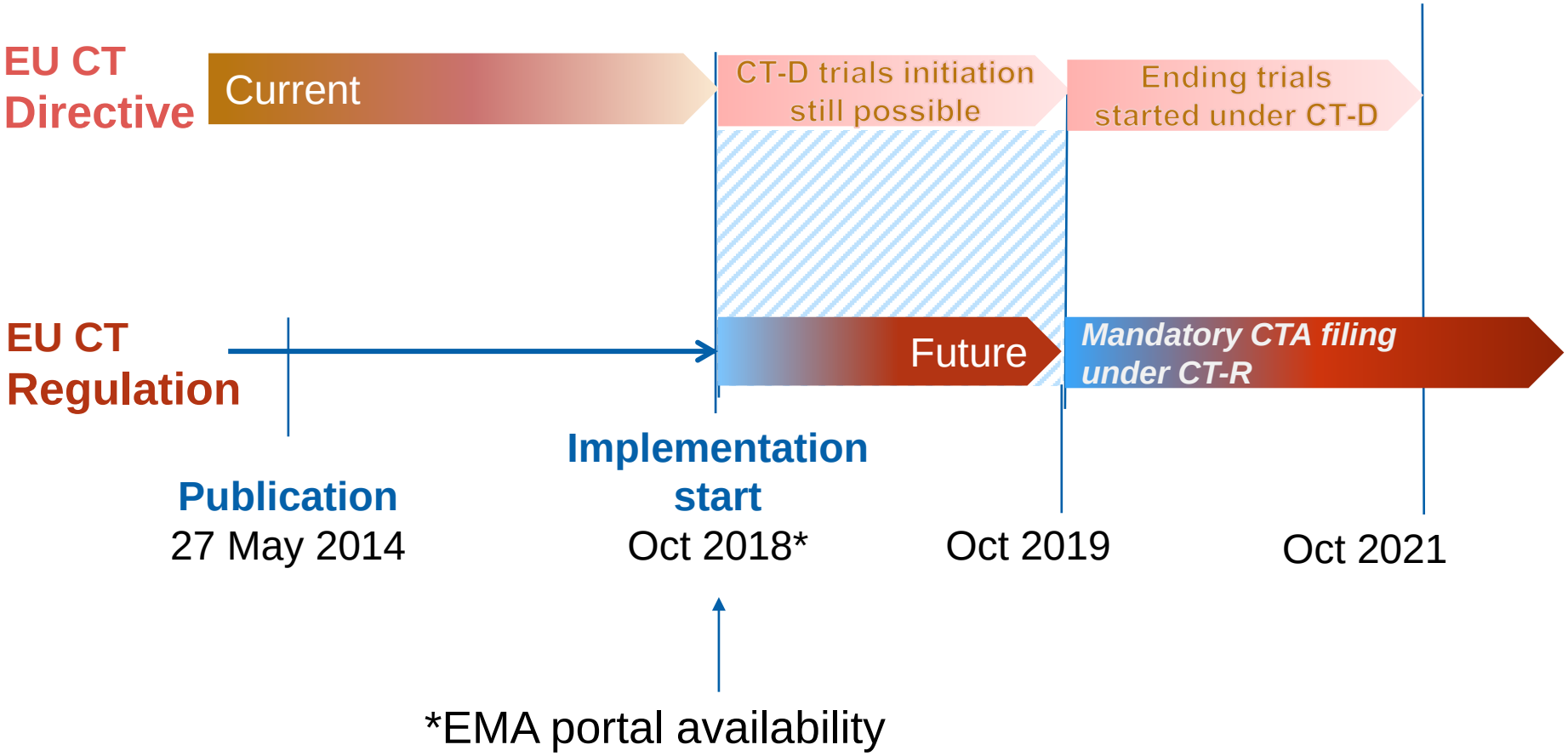


NOVARTIS

Cross-functional Implementation Core Team objectives

- Assess the impact of the regulation and changes needed to internal processes or new processes required
- Produce integrated recommendations for necessary changes, define implementation plans and make process changes in quality systems as required
  - Internal communication and training
  - Strategy for the transistion period
- Actively contribute to evolving regulatory landscape and as new guidance develops ensure internal recommendations and processes reflect these.

Transition phase provides for overlap of current and new processes



CTA: Clinical Trial Application
CT-D: Clinical Trial Directive 2001/20/EC
CT-R: Clinical Trial Regulation 536/2014

NOVARTIS

Key priorities and expectations in implementation

NOVARTIS

Implementation phase - Industry key priorities

- Development of EU Portal / EU Database
  - Functions – Use Case reviews
  - User Acceptance Testing
  - Stakeholder discussions
- Delegated acts and guidance
- Member states: National implementation phase
  - Monitoring and input in development of procedures
- Specific technical issues
  - Labelling of CT supplies
  - Lay summaries

NOVARTIS

Expectations

- Everything in place prior to implementation
  - Guidance / delegated acts finalised
  - Safety reporting system in place
  - Training in new processes for all stakeholders
- Technology/IT systems
  - Designed with end–users in mind
    - User-friendly interface and intuitive
    - Clear error messages
  - Appropriate access for MS stakeholders
    - Access to data does not delay assessment process
  - Processes facilitated by IT systems – flexibility
  - Opportunity to interact with system prior to implementation date

NOVARTIS

Expectations (contd)

- Consistent and predictable approach
  - Single set of data requirements for all MS for Part I assessment
    - No additional national requirements
  - Clear/ Consistent requirements from MS for Part II assessment
    - Available from a single source
  - Oversight to agreed standards / expectations
    - Training of assessors, inspectors etc
- Adherence to timelines
  - Acceptance of tacit approval
  - Acceptance of tacit withdrawal by sponsors

NOVARTIS

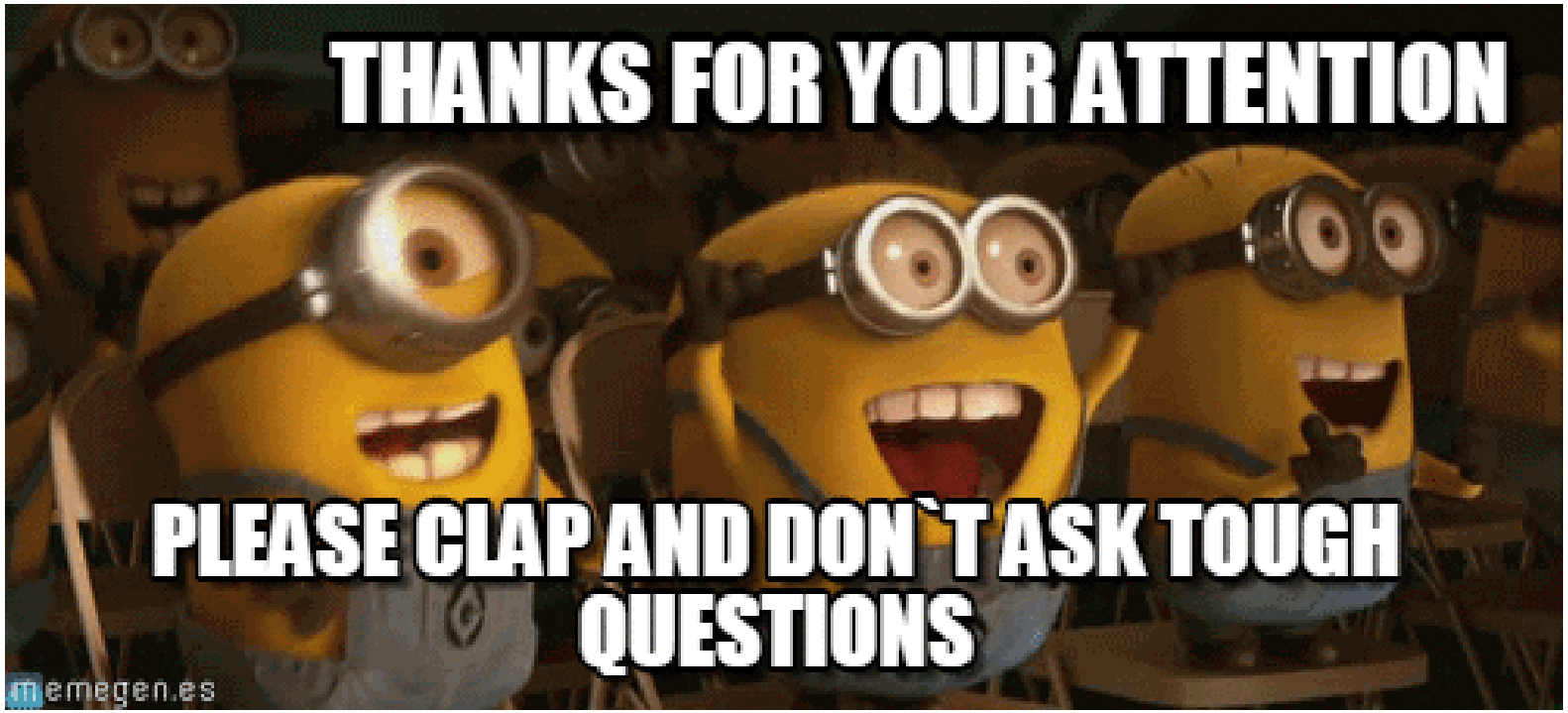
Concluding remarks

NOVARTIS

Conclusions

- New clinical trials Regulation is an opportunity
- High standards for conducting clinical research in Europe will be maintained
- A number of procedural issues and clarifications remain
- Simplification is welcome
  - Initially complex implementation....
  - ...followed by longer term realisation of advantages
- All stakeholders will need to embrace and work with new processes and thinking to ensure success

NOVARTIS


THANKS FOR YOUR ATTENTION
PLEASE CLAP AND DON`T ASK TOUGH QUESTIONS
memegen.es

NOVARTIS

Questions

Summary of overall timelines

	Validation (from submission)	Assessment (from validation to questions & reassessment of responses)	Clock Stop (Sponsor to answer questions)	Decision (from assessment)	Total
Initial Procedure (Part I & II)	**10 to 25 days**	**45 to 64 days**	**12 days**	**5 days**	**60 to 106* days**
Additional CMS (Part I & II)	**NA**	**52 to 71 days**	**12 days**	**0 days**	**52 to 83 days**
Substantial Modification (Part I & II)	**6 to 21 days**	**38 to 57 days**	**12 days**	**5 days**	**49 to 95* days**

* The rMS can additionally extend assessment time by 50 days for ATMPs and products derived from rDNA technology

- These represent maximum timelines, shorter timelines are possible