# Requirements for the reference safety information under the Clinical Trials Regulation

EC-DG SANTE/HMA-CTFG/EMA joint training on the Clinical Trials Regulation

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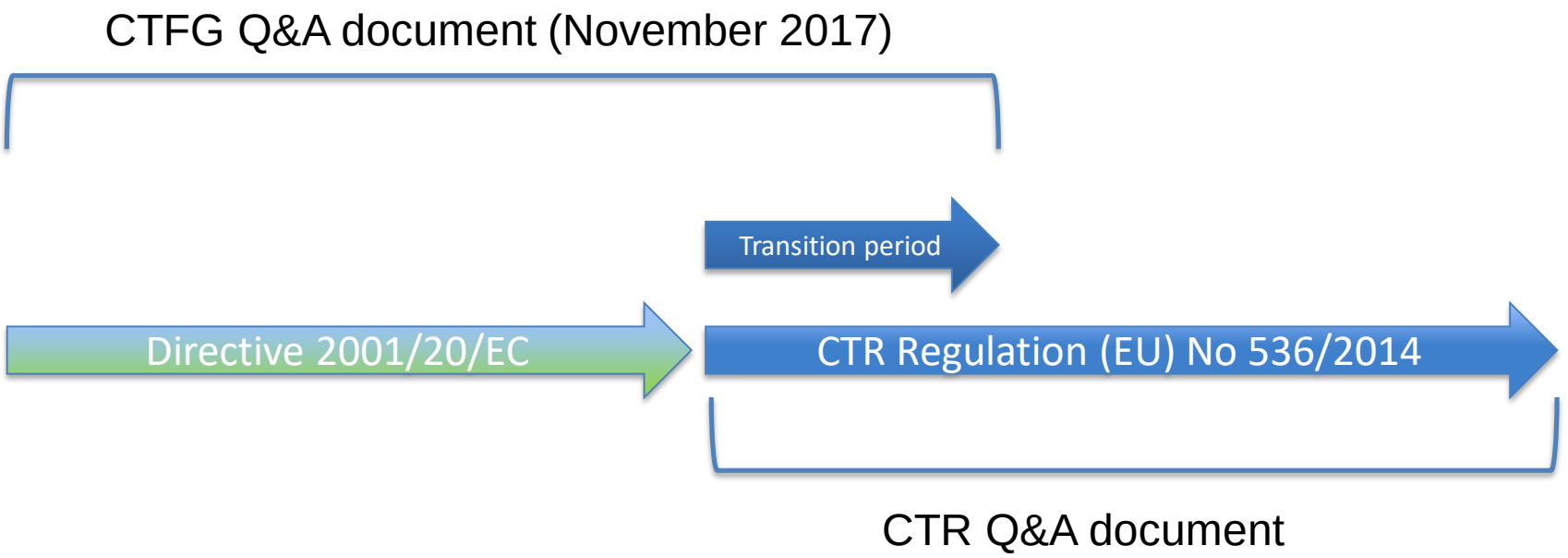
# Agenda

- New in CTR Q&A document
- Tips and tricks for the reference safety information (RSI) assessment
- Points that require attention and harmonization during clinical trial applications and substantial modifications assessments on the EU level

# Q&A documents: timelines of application:



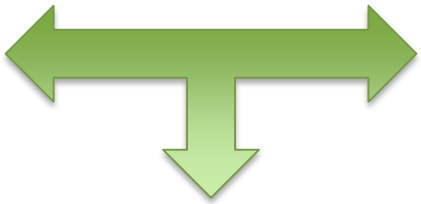

CTR Q&A document:
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
CTFG Q&A document:
https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

# Q 7.6: Serious vs. Severity

- Severity (intensity of an event) grading using CTCAE grading system: mild, moderate, severe
- Seriousness – outcome or action criteria→defines the regulatory reporting obligations

**Severe headache**

**Influences everyday activity**



**Does not require hospitalisation**

**Not serious, but severe**

# Format of the Reference Safety Information

**Table 1.0 Serious Adverse Reactions for the IMP considered expected for safety reporting purposes.**

| SOC | SARs | Number of subjects exposed (N) = 328 | | |
|---|---|---|---|---|
| | | All SARs | Occurrence of fatal SARs [1)] | Occurrence of life-threatening SARs [1)] |
| | | n* (%) | n (%) | n (%) |
| **Gastro-intestinal disorders** | Intestinal perforation | 9 (2.7) | 3 (0.9) | 6 (1.8) |
| **Hepatobiliary disorders** | ALT increase | 12 (3.6) | Not applicable | Not applicable |
| | AST increase | 9 (2.7) | Not applicable | Not applicable |
| **Cardiovascular disorders** | Myocarditis | 33 (10.0) | Not applicable | 2 (0.6) |
| | Bradycardia | (Rare) [2)] | Not applicable | Not applicable |

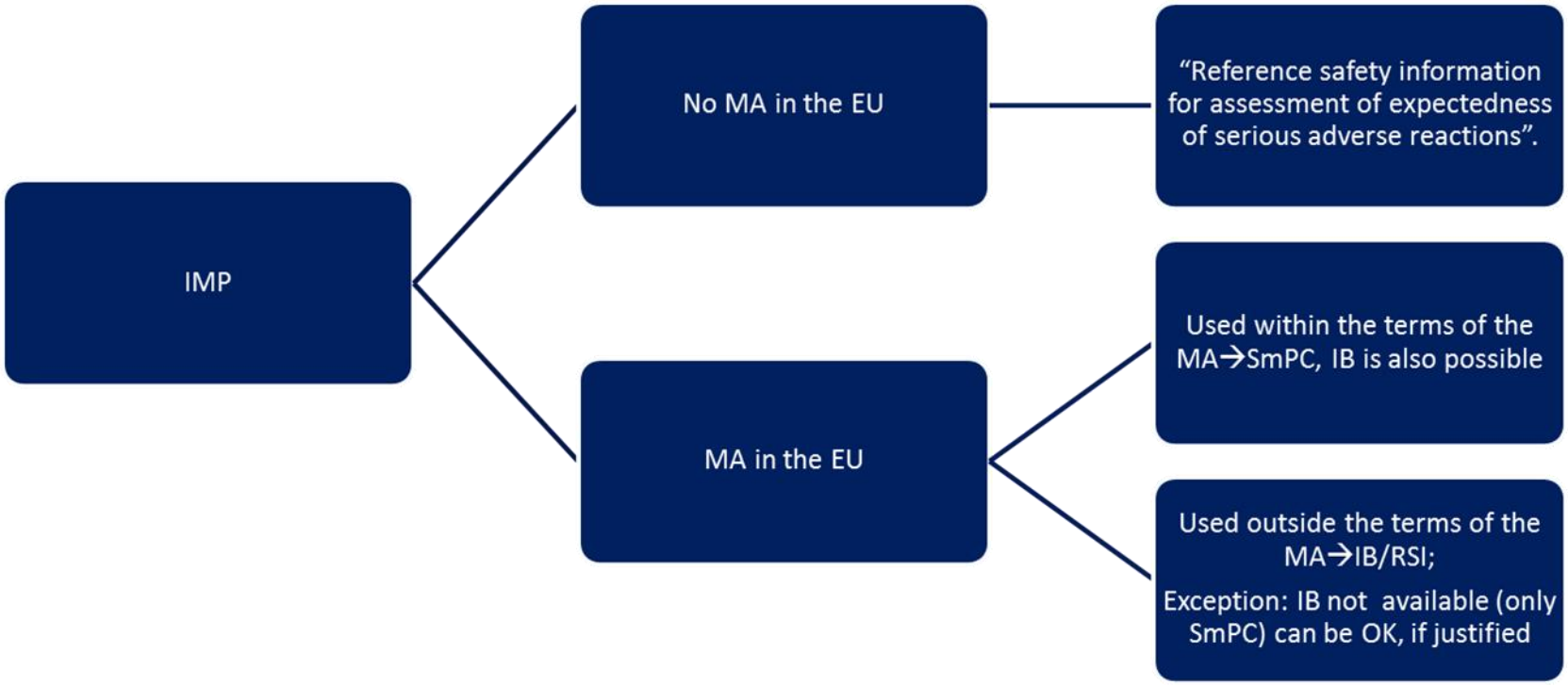
- It should always be clear if fatal and life-threatening SARs are considered expected
- Bradycardia seen in post-marketing setting only, not in clinical trials. Frequency calculated as per SmPC guidance: event not seen in 5460 subjects exposed in clinical trials. Post-marketing events were serious and occurred more than once.

# Justifications when updating RSI:

- Fatal SARs in the SmPC (section 4.8+text)→present, can be considered expected, More sensitive population - pediatric, fatal SARs should be considered unexpected
- Postmarketing SAR – if different indication/population from MA→justify
- Life-threatening SARs:

- Causality by sponsor and by the investigator, do they both agree?
- Non-serious ARs observed with the same MedDRA Preferred Term?frequency?
- Mode of action and class effect (simular is observed in the closely related IMPs), scientific articles
- If the IMP has a marketing autorisation in similar indication? Is SAR present in the SmPC?
- Risk mitigation measures (exclusion criteria, dose modification, discontinuation, exams)
- Patients are informed –ICF+ any other material for earlier detection
- B/R balance remains positive for the indication of the clinical trial

# Choice of the RSI: RSI in the IB vs. section 4.8 of SmPC




**Update!!!**

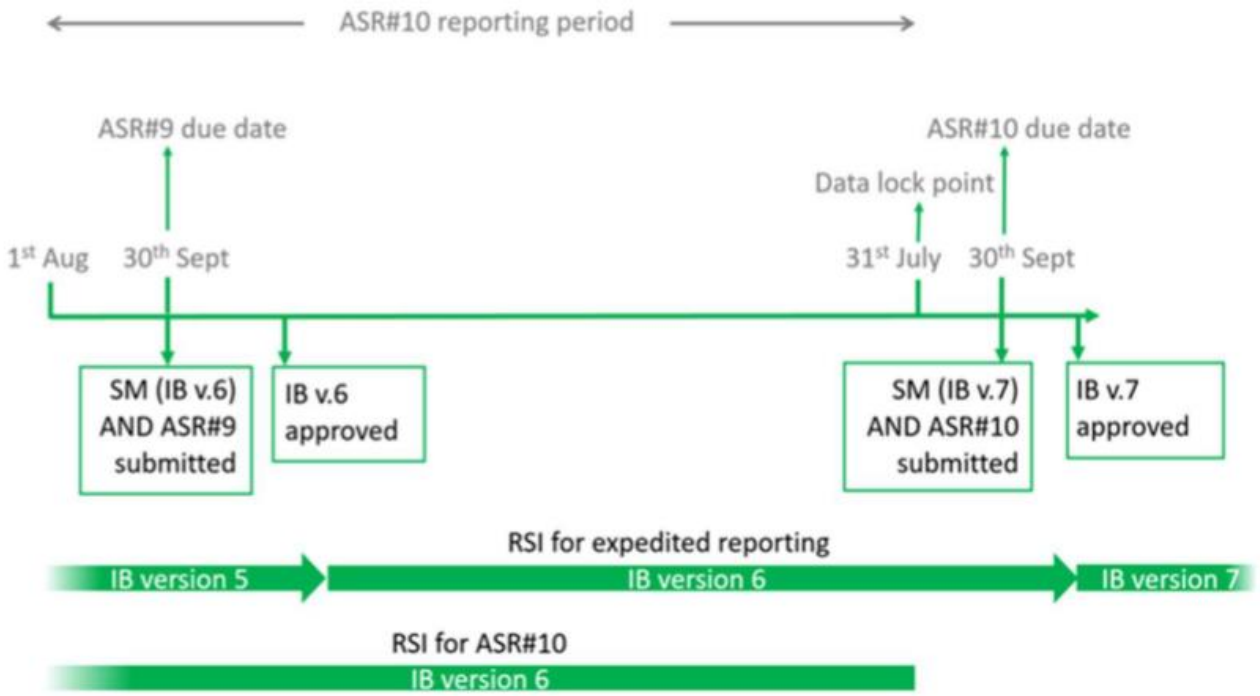
Positive opinion by the CHMP, but no commission decision or not yet marketed

the RSI in the IB

IMP outside MA→IB/RSI (several tables for different indications, if needed) or The SmPC section 4.8 if justified

# 7.15/205: ASR and an update of the RSI in the investigator's brochure

- It is highly recommended to **update the RSI section of the IB** (if necessary) **only once per year,** after the ASR data lock point, with the preparation of the ASR (ASR due date is 60 days after the Data Lock Point)
- **Substantial modification (SM) for all trials that use the IB →all EU Member States where trials are ongoing in parallel with the ASR submission**
- New RSI→approval by all MS →to approved by at least one MSC for the trial→ use for assessment of expectedness (**not yet approved→SUSARs**)



# Tips and tricks for the assessment of a substential amendments:

Is RSI clearly identified? (cover letter?)If SmPC section 4.8 is used?Separate document?Appropriate for this population/indication?

new SARs (risk mitigation measures)→check→ protocol needs update?→ if not→cover letter

Classification by SOC?SARs presented with PTs?

Frequency-present including SARs from postmarketing experience (not known is not acceptable)?Is it based on SARs?

Does it include expected SARs only?Do any SARs=1? Fatal (only for MA in EU)? life-threatening? Justification provided?

# Main concerns based on recent inspections:

- The RSI version applied from case receipt date and not the onset date.
- The sponsor of a trial has a duty to report SUSARs relating to each IMP used in a clinical trial, therefore, also relating to the comparator(s). The changes to the SmPC should be acknowledged to protect the safety of the trial participants.
- Implementation of a substantial amendment prior to NCA approval IB/RSI approved for one trial but not for the other
- SmPC section 4.8 copy pasted in the IB, no rational is provided.
- Disease progression/death and study endpoints→protocol: the investigator →SAE assessment of relatedness (more severe than expected in trial population?)→yes→SUSAR; -death: disease progresson only-->SAE, death-->IMP-->SUSAR

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