Bundesamt für Sicherheit im Gesundheitswesen
BASG

EC-DG SANTE/HMA-CTFG/EMA joint training on the Clinical Trials Regulation (EU) 536/2014

National aspects in the CTR and Member State preparedness

Stefan Strasser, MD

Department Clinical Trials, Austrian Medicines and Medical Devices Agency

Disclaimer

Bundesamt für Sicherheit im Gesundheitswesen
BASG

The content of this presentation reflects the personal knowledge, experience and view of the author.

It does not necessarily represent the view of the Federal Agency for Safety in Health Care (BASG), the Austrian Agency for Health & Food Safety (AGES), the European Medicines Agency (EMA) or the European Commission (EC).

Any omission or truncation of regulatory requirements found within this presentation does not relieve any entity or person of their legal obligations to fully comply with all applicable regulatory requirements.

Overview

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- National legislation superseded by CTR
  → **no change possible**
  → **flexibility in some points**

- European or national legislation with interface to CTR
  → **no change necessary**

- National legislation impacted by CTR
  → **need for revision/new legislation**

National legislation superseded by CTR

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Passages from National legislation that are now fully covered by Regulation 536/2014 will have to be removed.

- *Definitions → clinical study, clinical trial, non-interventional study, auxiliary medicinal product*
- *Submission process → single submission, use of CTIS*
- *Process Timelines*
- *Harmonisation between Member States (RMS/MSC worksharing)*
- *Dossier requirements (Annex I)*
- …

Some flexibility remains…

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Informed consent:
  - Qualification of the interviewer (Recital 30)
  - Determination of the legally designated representative (Recital 27)
  - Signatures of incapacitated subjects (Article 39, section 7)
  - Assent of minors (Recital 32)
  - Simplified consent for Cluster trials (do not exist in AT) (Article 30)
- Investigator qualification and training (Article 49)
- Setting up a legal representative (Article 74)
- Vulnerable populations:
  - Direct benefit for incapacitated subjects (Article 31, section 2)
  - Prohibited populations (Recital 35)

CTR interface to other legislation

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Topics affected:

- Definitions from other laws (Minor, Incapacitated subject, Legally designated representative)
- Legislation on medical devices and in-vitro diagnostics
- Genetically modified organisms/GMOs („Gentechnikgesetz")
- General Data Protection Regulation (GDPR)
- Liability by civil or criminal law („Strafrecht", „Zivilrecht")
- Handling/archiving of medical files („Krankenanstaltengesetz", „Ärztegesetz")
- Manufacturing requirements/GMP („Arzneimittelbetriebsordnung/AMBO")
- Regulations for special types of products (narcotics, abortifaciens, embryonal stem cells…)

National legislation impacted by CTR

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Non-interventional studies (including possibility for inspection)
- Ethics committee (IEC) organisation/interaction with NCA
- Single decision
- Safety assessment
- Exceptions from Manufacturing/Import Authorisation
- Single fee
- Damage compensation
- Language
- Penalties

Non-Interventional Studies (NIS)

Bundesamt für Sicherheit im Gesundheitswesen
BASG

A NIS currently and in future does not allow

- use of unauthorised products
- assignment to a treatment strategy in advance
- to make prescription dependent on inclusion
- to perform additional diagnostic/monitoring procedures

Austria has a national regulation to report NIS to the agency to be published in a public registry.

Currently the product needs to be prescribed **within the terms of the marketing authorisation (= SmPC)**.

For the CTR the use of the product only needs to fall **within normal clinical practice of the MSC**.

This would allow NIS for established off-label use in routine clinical care.

EC QnA 1.7 on clinical practice

Bundesamt für Sicherheit im Gesundheitswesen
BASG

*"With regard to off-label use of medicinal products with a marketing authorisation in the EEA it is **within the competence of each Member State** to determine if established off-label use in principle is considered within their normal clinical practice and can be investigated in a non-interventional study or not.*

Sponsors are recommended at the planning stage of such a clinical study/clinical trial to seek advice from all Member States where the study/trial is intended to take place. A clinical trial application should then be submitted to all Member States where the conduct of a non-interventional study is not possible."

NCA & IEC Organisation

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Recital 18:

*It should be **left to the Member State concerned to determine the appropriate body or bodies to be involved in the assessment** of the application to conduct a clinical trial **and to organise the involvement of ethics committees** within the timelines for the authorisation of that clinical trial as set out in this Regulation. Such decisions are a matter of internal organisation for each Member State.*

Recital 69:

*Within a Member State, there may be several bodies involved in the authorisation of clinical trials. In order to allow for effective and efficient cooperation between Member States, **each Member State should designate one contact point**.*

Article 2, section 2 (11):

*'Ethics committee' means an **independent body** established in a Member State **in accordance with the law of that Member State** and **empowered to give opinions** for the purposes of this Regulation, **taking into account the views of laypersons, in particular patients or patients' organisations.***

Article 4:

*A clinical trial shall be subject to scientific and ethical review and shall be authorised in accordance with this Regulation. **The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned.** The review by the ethics committee may encompass aspects [of Part I and part II] as appropriate for each Member State concerned.*

*Member States shall ensure that the **timelines and procedures for the review by the ethics committees are compatible** with the timelines and procedures set out [in the Regulation].*

Single decision

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Medicinal Product Act

Regional laws for Ethics Committees

General Administrative Procedure Act

- Define National contact point
- Define interaction between NCA and IEC
- Define IEC composition and process (other laws involved!)
- Establish a workflow with national tasks and timelines within the CTR timelines
  → National IT system?

- Establish procedure for legal (positive or negative) decision within five calendar days (especially if you are not the deciding authority)
- Establish a procedure for appeal

- Similar procedure for substantial modifications

Safety Assessment

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Article 44
Assessment by Member States

1. The Agency shall, by electronic means, forward to the Member States *concerned the information reported in accordance with Article 42 [**SUSARs**] and 43 [**DSUR**].*

2. Member States shall cooperate in assessing the information reported in accordance with Articles 42 and 43. *The Commission may, by means of implementing acts, set up and modify the rules on such cooperation. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 88 (2).*

*3. The **responsible ethics committee shall be involved** in the assessment of the information referred to in paragraphs 1 and 2, **if it has been provided for in the law of the Member State concerned**.*

- CTFG projects ongoing (DSUR worksharing…)
- Delegated act in preparation
- „Neglected child“ of the clinical trial family?

Delegated Act (CTR)

Medicinal Product Act

Exceptions from MIA

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Article 61

5. Paragraph 1 shall not apply to any of the following processes:

(a) ***re-labelling or re-packaging*** *[…]*

(b) ***preparation of radiopharmaceuticals used as diagnostic investigational medicinal products*** *[…]*

(c) the ***preparation of medicinal products referred to in points (1) and (2) of Article 3 of Directive 2001/83/EC for use as investigational medicinal products*** *[…]*

[…] where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons ***legally authorised in the Member State concerned*** *to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State;*

6. ***Member States*** *shall make the processes set out in paragraph 5* ***subject to appropriate and proportionate requirements*** *to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to* ***regular inspections.***

- What are **„appropriate and proportionate“** requirements?
- What is **„regular“**?
- Harmonised and transparent standards?

Medicinal Product Act

Manufacturing Site Act

Single fee

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Recital 71:

*In order to carry out the activities provided for in this Regulation, **Member States should be allowed to levy fees**. However, **Member States should not require multiple payments to different bodies** involved in the assessment, in a given Member State, of an application for authorisation of a clinical trial.*

Recital 81:

*As regards Directive 2001/20/EC, experience also shows that a large proportion of clinical trials are conducted by non-commercial sponsors. Non-commercial sponsors frequently rely on funding which comes partly or entirely from public funds or charities. In order to maximise the valuable contribution of such non-commercial sponsors and to further stimulate their research but without compromising the quality of clinical trials, **measures should be taken by Member States to encourage clinical trials conducted by those sponsors.***

- Define **distribution of fees** between NCA and Ethics Committee
- Define fees **for different roles** (RMS, CMS, subsequent MS)
- Define fees for **Part I and Part II**
- Define **special fees for non-commercial trials?**

Medicinal Product Act

Fee Regulation

Damage compensation

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Recital 61:

In clinical trials compensation should be ensured for damages successfully claimed in accordance with the applicable laws. Therefore Member States should ensure that systems for compensation for damages suffered by a subject are in place which are appropriate to the nature and the extent of the risk.

Article 76

Damage compensation

*1. Member States shall ensure that **systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place** in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.*

*2. The sponsor and the investigator shall make use of the system referred to in paragraph 1 in the form **appropriate for the Member State concerned** where the clinical trial is conducted.*

*3. Member States shall **not require any additional use of the system** referred to in paragraph 1 from the sponsor for low-intervention clinical trials, **if** any possible damage that could be suffered by a subject resulting from the use of the investigational medicinal product in accordance with the protocol of that specific clinical trial on the territory of that Member State is **covered by the applicable compensation system already in place.***

Medicinal Product Act

Language requirements

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Recital 26:

*It should be left to Member States to **establish the language requirements for the application dossier**. To ensure that the assessment of the application for authorisation of a clinical trial functions smoothly, **Member States should consider accepting a commonly understood language in the medical field** as the language for the documentation not destined for the subject.*

Article 26
Language requirements

*The **language of the application dossier**, or parts thereof, **shall be determined by the Member State concerned**.*
*Member States, in applying the first paragraph, shall consider accepting, for the documentation not addressed to the subject, a **commonly understood language in the medical field**.*

Article 69
Language

*The **language of the information on the label shall be determined by the Member State concerned**. The medicinal product may be labelled in several languages.*

IECs request German summary for protocols in English.
Discussion about benefit/risk description.

Medicinal Product Act

IEC guidances?

Penalties

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Article 94
Penalties

*1. Member States shall lay down **rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented.** The penalties provided for shall be effective, proportionate and dissuasive.*

2. The rules referred to in paragraph 1 shall address, inter alia, the following:

(a) non-compliance with the provisions laid down in this Regulation on submission of information intended to be made publicly available to the EU database;

(b) non-compliance wit the provisions laid down in this Regulation on subject safety.

- Implemented in the Austrian Medicinal Products Act.
- Currently not part of legal practice

Medicinal Products Act

Administrative Procedure Penalty Act

Clinical trials according to drug and device legislation

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Example for interface within NCA/department

Medicinal Products Act
Medical Devices Act

Nature of the product?
Scope of the investigation?

Medicinal Product

Regulation 536/2014

Authorised yes/no
Within SmPC yes/no

Medical Device/IVD

Regulation 2017/745 or 2017/746

CE-marked yes/no
Within Intended Use yes/no

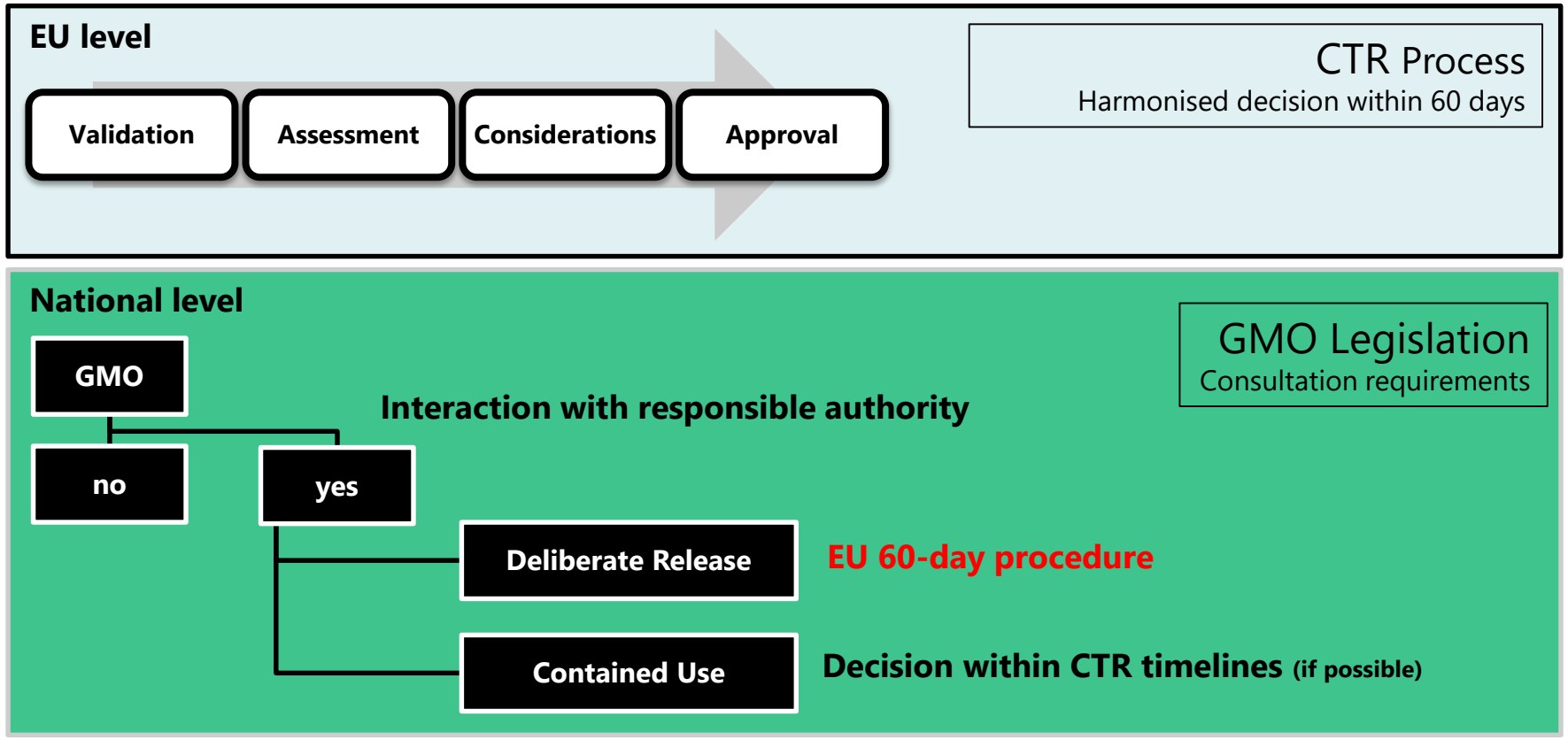
Drug vs. Device
Non CE-marked Device
Device outside Intended Use

different legal frameworks and procedures
(in some member states different authorities)

CTs according to medicines and GMO legislation

Example for decision by two independent authorities

Bundesamt für Sicherheit im Gesundheitswesen
BASG



Bundesamt für Sicherheit im Gesundheitswesen
BASG

Thank you for the attention!

Questions?

Austrian
Federal Office for
Safety in Health Care

BASG

Stefan Strasser, MD

Head of Clinical Trials

BASG -
Austrian Federal Office for Safety in Health Care

Traisengasse 5
1200 Vienna

stefan.strasser@ages.at

www.basg.gv.at