Impact of the Directive 2001/20/EC on the clinical trial regulation in Hungary

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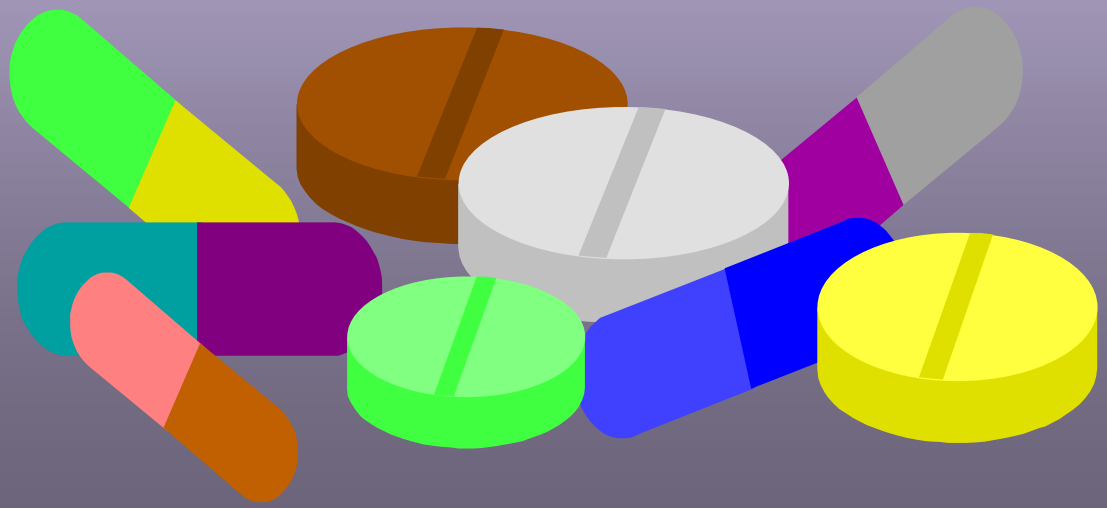


What were the main objectives of the Directive 2001/20/EC?

harmonize: the EU Clinical Trial (CT) regulations (administrative procedures timeframes etc)

promote: the highest ethical standards for all of the participants (esp. for the vulnerable patients)

What were the main objectives of the Directive 2001/20/EC? (cont.)

provide: statutory basis for
- Ethics Committees (EC)
- Competent Authorities (CA)
- GCP/GMP

lay down responsibilities:
- inspection,
- AE/AR reporting
- CA in internal communication and processes

"Test questions" (How successful has been the implementation of the Directive?)

- What is the role of the Competent Authority (CA) in clinical trial regulation?
- Is it consistent with the procedures and time scales specified in the Directive?
- Is there a parallel process for regulatory approval and ethical opinions?
- Is there a process for single ethical opinion in multi centre trials.

"Test questions" (How successful has been the implementation of the Directive?) (cont.)

- Are there any regulations related to trials in special populations (re: Art 4 and 5)
- Is there GMP regulation in place and does it cover also the investigational products?
- Do requirements for safety reporting include SUSAR-s, which have to be reported within 7/15 days to CA and EC-s?
- Has the GCP inspection been implemented?

I am going to speak about:

- the authorisation of CT-s in Hungary (the role of the Competent Authority)
- the function of EC-ies
- protection of clinical trial subjects
- notification of SUSAR-s
- GMP
- Inspections
- Experiences
- Forthcoming tasks

What has already been done?

(in the field of regulation)

What has already been done?

In the field of

regulation:

- **updating of national legislation in line with the requirement of the Directive**
- **implementing the timeframe for authorisation/ethical approval of CT-s**

Clinical Trial Regulation in Hungary

- The clinical trials (CT) have been regulated since the 70-s
- The basis of the present system was laid down in 1987 (Min.Decree 11/1987)
- The principles, requirements and guidances of the Directive 2001/20/EC have been transposed into Hungarian legislation /Min.Decree 24/2002 (V.9) /

Legal “source” documentation's of 24/2002 (V.9.) Ministerial decree

- Act CLIV of 1997 on Health
- Act XXV of 1998 medicinal product for human use
- Act VI 2002
  - Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Oviedo Convention)
  - Convention on Human Right and Biomedicine

Scope

(Article 1.)
Directive 2001/20/EC

- The Scope of the Decree is identical with that of the Directive.

  (new: IV. phase CT included)

- The GCP/GMP are biding by law.

Authorisation of CT-s in Hungary

(Article 9 competent authorities)

7. § Decree 24/2002 (1-6)
and Act XXV of 1998 (Art.10 (5)

- All CT-s have to be authorised (by the National Institute of Pharmacy) (NIP)
- approved previously by the Central Ethics Committee (CEC)

Documentations requested for CT authorisation by the NIP

(Annex 2. Min. Decree 24/2002)

- Application format (filled in)
  (EU format accepted)
- Study protocol
- CRF
- Invest. Brochure
- Patient information/Informed consent
- Signatures and CV-s of the investigators
- Permission of the director of the hospital

Documentations requested for CT authorisation by the NIP (cont.)

(Annex 2. Min. Decree 24/2002)

- Insurance certificate
- Costs of CT: division of payment between hospital and investigators
- Chemical/pharmaceutical documentations
- GMP/TSE certificates

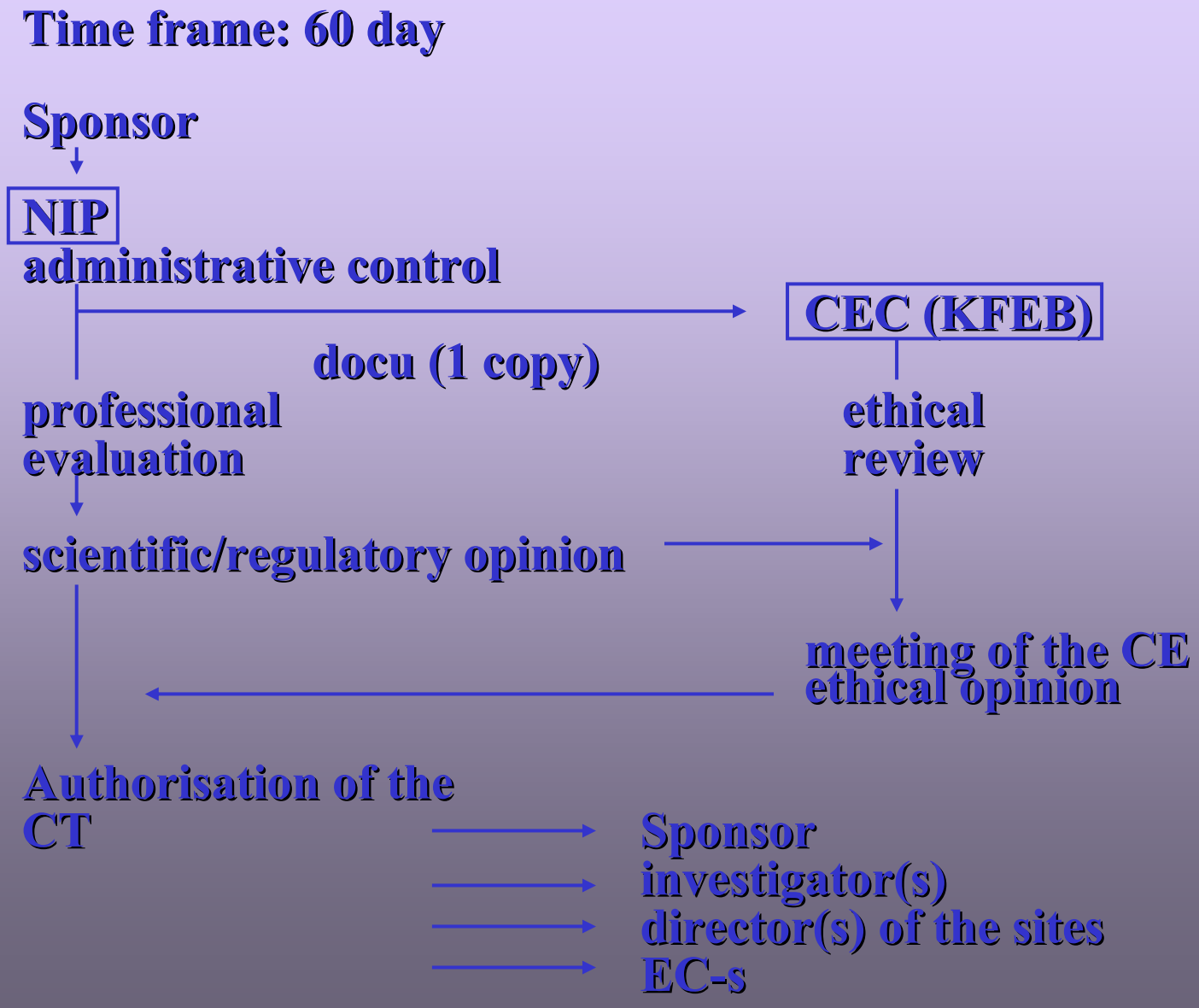
-*-

- one package of the invest. product used in the CT

The NIP evaluates the documents

- completeness (one copy → Central EC)(48-74^{h})
- scientific value and justification of the project
- suitability of the protocol
- feasibility (personal/material)
- quality of the Invest. Med. Product
- Authorisation of the CT (time frame: 60 days, provided that both opinions (CEC and NIP) are favourable.

Flow diagram of the CT authorisation procedure in Hungary



Ethical Control of CT-s in Hungary

2-tier system exists:

1. **Central/national/, Independent Ethics Committee**
   (composition, operations procedure, duties are in accordance with the GCP rules)

↓

Single Ethical Opinion on the trial

↓

2. **Local Ethics Committee(s)**
   main tasks: opinion:on the feasibility (staff+facilities)
   continuous monitoring of the trial

Single Opinion of th EC

Dir. Art. 7.

For multi.centre trials MS shall establish a procedure providing for the adoption of a single ethical opinion for that MS

But: No guidance on how single opinion will be obtained in MS-s.

Ethics Committee (Article 6.)

8. § (1-4) Min. Decree 24/2002.

Central EC (KFEB)

Duties:

- **to prepare ethical opinion(s) on issue requested (before commencement of a CT)**
- **in preparing its opinion the main points to be considered are essentially similar to those notified in the Article 6 (Directive 20/1001)**
- **may request for more/special information**

What are the new points?

- personal and material conditions of the CT-s
- insurance or indemnity to cover the liability of the investigator/sponsor
- financial issues
  (e.g. rewarding/compensating investigators/ trial subjects, financial agreement between the sponsor and the site)
- recruitment's of subjects
- use of placebo

Special attention: to minors/incapable patients

- Act CLIX Eütv. (4.7.5.)
- 24/2002. Min. Decree (15 § 1-6)

Annex No 1 24/2002. Min.Decree

Personal and material conditions of CT-s

a.) Clinicopharmacological sites
(separated from rutin health care)
- in hospitals with intensive Dpt.
- staff:
  - main investigator (M.D.)
    scientific degree, specialist
    GCP certificate
  - others M.D.
    specialists
    GCP certificate
    experts in emergency

Annex No 1 24/2002. Min.Decree (cont.)

Personal and material conditions of CT-s

b.) Clinical-investigational sites

- hospitals, outpatient clinics GP consultations rooms
  (GP-s must have a contract with a hospital for emergency care)
- staff: M.D.-s
  experience
  GCP certificate

Protection of clinical trial subjects

(Article 3.)

Act on Health (1997)

159 § (More detailed and more comprehensive then the (Article 3)

(on the general conditions and requirements of conducting CT-s)

- justification of the objectives of the CT
- suitability of the protocol
- preliminary results (effectiveness/safety) are favoruable
- acceptable risk/benefit ratio
- protection of the trials subjects

etc.

3. § Conditions of participation in CT-s Decree 24/2002 3. § (1)

- the necessary medical care be ensured for all participants
- fertility, pregnancy (in the future) should be considered,
- the possible pain, anxiety, harm of the subject should be minimised
- the health of the subject should be continuously monitored (controlled)
- the recruitment of the subjects and their compensation should be regulated

4. § 1-4. Min. Decree 24/2002. Information of the participants

- Is the subject mentally capable?
- The content of the information (written)
  - identification of the trial
  - nature, purpose of the study
  - the possible alternative treatment
  - inconvenience, possible harm, adverse reactions, and benefits
  - randomisation / the chance in % receiving placebo
  - insurance, compensation, indemnity
  - emphasis on volunteeriness, right to withdraw
  - the confidentiality of the data
  - the name of contact person and his availability (member of the local EC)
  - information about the invest. product

4. § 5. Min. Decree 24/2002. Informed consent

- "in written form"
- the content of the consent (detailed)
- dated
- signed by the: trial subject and
  the investigator
  legal representative*
  witness (if necessary)*

Provisions:

- in case if the subject not able to read
- new consent is necessary if new, substantial information obtained.

* if applicable

Minors and incapacitated adults
5. § 1-6.

The text is similar to that of Article 4/5 of the Directive

- informed consent of the parents/legal representative should be obtained and must represent (also/the minors) incapacitated adults will.
- Information (given by person with experience) according to their capacity of understanding
- the risk threshold and degree of distress should be constantly monitored
- EC-s with special expertise (with expertise /in paediatrics or psychiatry/ has endorsed the protocol)

Connection between NIP and CEC

- the CEC is an absolute independent body (supervised only by the Min. of Health)
- the evaluations of the protocol (other docu.) carried out parallel by the CEC
- NIP has to focus on the regulatory, professional, scientific issues, CEC on the ethics
- the NIP → submit its a review to the CEC, 10 days before the next meeting
- the authorisation (granted by the NIP) contains the ethical approval of the CEC

Amendments to the authorisation 18. § 1. Min. Decree 24/2002

sponsor:

- has to notify the NIP (the reason and content of the amendment)
- new patient inform. should be enclosed (of the risk/benefit changed)

NIP:

- authorization is released if the EC's opinion is also favourable

Suspension of CT

17 §. Min. Decree 24/2002

The NIP may suspend or prohibit the CT if there are problems about the

- **conditions of CT**
- **safety of the subjects**
- **scientific validity of CT**

NIP: notify the sponsor / investigator(s)
answer: within 8 days

NIP notify → Central EC
→ Local EC
→ ANTSZ*

* Natl. Med. Chief Officer's Office

Suspension of CT
(cont.)

(17 §. Min. Decree 24/2002)

If the sponsor wants to suspend the CT, should notify (and explain)

→ NIP → Central EC

→ investigators

The text ≈ similar to that of the Directive

(Article 12)

Reporting on the end of the CT

(Article 10)

(19/20 §. Min. Decree 24/2002)

investigator:

- **content: Number of the participants, "relevant events"**
- **time frame: 90 days (of the end of the CT)**
- **→ NIP/CEC**

sponsor:

- **early termination report**
  - **content ("explanation")**
  - **time frame: ≤ 15 days**
  - **→ NIP/CEC /investigators**
- **final report**

Notification of Adverse Event/Reaction

(Direct Article 16)
13 §. 1. Min. Decree 24/2002 } the two texts are essentially similar

investigator: to report

- all Serious AE/AR immediately to the sponsor (unless identified otherwise in the IB (protocol) and the local EC
- follow up information
- other AE → sponsor (within the time periods, specified in the protocol)
- in case of death → sponsor
  → EC
  → Local EC
  time frame: 15 days
- sponsor: shall keep detailed records of AE
  → NIP (on request)

Reporting of SUSAR-s and SAR-s (newest version)

- **SUSAR-s:**
  sponsor: → NIP/CEC
  → other concerned CA-s/EC-s
  → investigators
  → EU database
  time frame: SUSAR (life threatening)
  7 days + 8 days (follow up rep.)
  other SUSAR: 15 days
- **Annual report (SAR + SUSAR)**
  → NIP/CEC
  → other concerned CA-s/EC-s
- **Safety Alert (if necessary)**

Manufacturing and labelling of the Investigational Medicinal Product

11 §. 1. Min. Decree 24/2002

- Manufacture, labelling, storage, records, etc. refers to Government Decree 37/2000.

Inspections
15 § 1.

- NIP controls (by appointed inspectors)
  → GMP
  → GCP rules
  (inspected sites:
  trial, manufacturing sites, laboratories)
  prepares inspection report
- ANTSZ controls
  - the health care of the trial subjects
  - suitability of the staff/facilities
  - insurance conditions
    institutional pharmacy
  - protection of personal data
- EC-s (Central/local)
- OEP (Nat. Health Insurance Fund Adm.) controls financial contracts

Issues which have not been authorized yet.

Problems/Experiences

Central Ethics Committee//NIP

- **"single request" for supplementary information and single answer from the sponsor within 30 days (Article 6.6.)**
- **"no extension to the 60 day period except…..for special products" (Article 6.7.)**

These procedures have not yet harmonized!

Solution:

- **the recommendations of the Directive be followed in the practice**
- **amend the Min Decree 24/2002**

Problems/Experiences

To keep the 60 day time frame for authorisation / ethical approval procedure?

Yes (!) - in the majority of the cases

Problems:

- **the frequency of the CEC meeting (once/month)**
- **the CEC overburdened (20-25 items/meeting)**
- **the submitted documentations are often incomplete**

Problems/Experiences

The local EC-s often misunderstand their legal duties and function (!), which are:

- **opinion about the local feasibility of the project (personal + facilities)**
- **monitor the ongoing studies**
- **to give independent information to the participants (on request) and to the director of the hospital**

<u>solution:</u> - to offer proper training for the members of the local EC-s

- issue a new regulation on the activity of the local EC-s (happened)

Issues which have not yet harmonised

- **Nomination of qualified persons**
  (Art. 2.-3.)
  (appointment, responsibilities, qualification etc.)

solution:

- **the Hungarian practice should follow the requirements of the Directive**
- **the Min. Decree be amended**

Issues which have not yet harmonised

Conduct of Clinical Trial (Article 10.)

- time frame for approval of a protocol amendment

Solution:

- the NIP keeps the 35 day deadline for the approval-procedure (as it recommended by the Directive)
- amend the Min.Decree 24/2002

International Connections
(EU. data-base)

Eudra CT number

- Application Form
- (I.) Opinions of the:
  - Competent Authority (CA) : pos/neg - reasons
  - Ethics Committee (EC) : pos/neg - reasons
- Authorisation of substantial amendment
  - CA : pos/neg - reasons
  - EC : pos/neg - reasons
- Declaration of the end of the clinical trial

Number of CT-s in Hungary

	1996	1997	1998	1999	2000	2001	2002	2003	2004 5mths
I	1	2	5	6	4	7	13	8	5
II	16	26	25	24	27	37	39	54	26
III	84	101	148	141	164	129	131	111	64
IV	63	71	74	72	50	39	29	22	11
Equiv	8	24	17	12	12	14	18	8	3
Noninterventional				22	33	72	48	52	28
Total	172	224	269	277	290	298	278	255	137

Thank you for your attention