

Clinical Research Law in Central Europe: Compliance Issues and Opportunities for Asian Biotech Companies

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Clinical trial regulatory issues according to the 2001/20/EC Directive and the Hungarian example

Any test made on humans, and qualified as a medical research, at one or more testing places, the aim of which is to

- aa) explore the clinical, pharmaceutical, or pharmacodynamic effects, or to
- ab) identify undesirable medical effects, or
- ac) study the absorption, distribution, metabolism and secretion of one or more investigational medicinal products in order to confirm the harmlessness, efficiency, advantage/risk ratio of the product,
- excluding assays not involving interventions;



Not qualified as clinical trials...

those non-interventional trials in which:

- a) the drug is ordered not for the purpose of the test, and
- b) the drug is ordered in a way common in the clinical practice, in accordance with the terms of the license for release, and
- c) the involvement of the patient in a given treatment strategy is not preliminarily specified in an protocol, instead the drug is ordered in a way complying with the actual clinical practice, and the order is clearly separated from the decision on the involvement of the patient in the investigation, and
- d) no additional diagnostic or monitoring procedure is used on the patient beyond the usual clinical practice, and
- e) exclusively epidemiological methods are used for the analysis of the collected data.



Investigator

- who is responsible for the conduction of the clinical investigation at the testing place



Principal investigator

- the responsible leader of the group at a given testing place if the clinical trial is made by a group of several investigators



Principles

- principles of the good clinical practice (GCP)
- ethical principles of the medical research (Helsinki declaration)
- the detailed guides published by the European Commission
- directives and regulations of the EU
- rights, safety and welfare of the subject



Subject

- a person involved in the clinical investigation on whom the investigational medicinal product is applied, or who takes part in the investigation as a control person



Subject

mentally competent persons

- written information
- declaration of acceptance
- protection of data

persons of minor age and incompetent persons of major age

- generally cannot be subject
- just in case the defined conditions meet



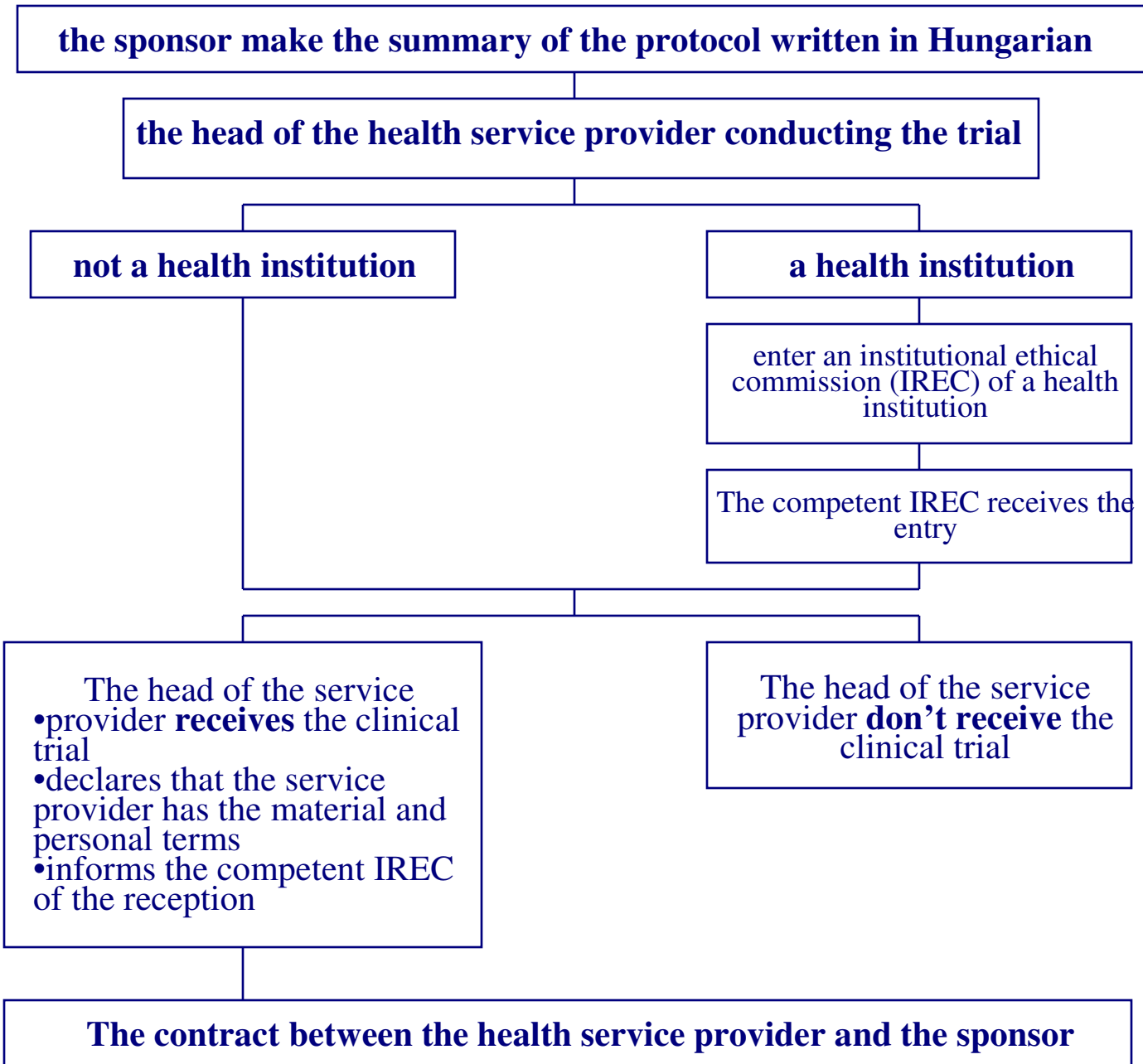
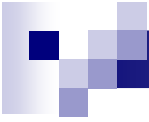
Sponsor

- initiates, conducts or finances the clinical trial
- the sponsor remains responsible for the observance of regulations if he appoints somebody to perform certain or all duties relating to the trial
- **in case the sponsor is not settled in a member state of the EER Agreement, its legal representative must be settled in a member state of the EER Agreement (i.e. For Asian Biotech Companies and Pharmaceutical Manufacturers)**



Application for the official licence

protocol: a document containing the purpose, arrangement, methodology, statistical considerations and organisation of the investigation which contains inclusion and exclusion criteria relating to the subjects, the principles of monitoring and publication, including any consecutive versions and modifications of the protocol



Sponsor must submit in two copies

- the application for the licence on a data-sheet downloadable from the webpage of the EMEA
- appendixes to the application form
- Receipt of confirmation of EudraCT Number
- Covering letter
- Application form
- Disk with XML file for EudraCT
- Protocol with all current amendments
- Investigator's Brochure
- Investigational Medicinal Product Dossier (IMPD)
- Simplified IMPD for known products
- Summary of Products Characteristics (SmPC) (for products with marketing authorisation in the Community)
- List of Competent Authorities within the Community to which the application has been submitted and details of decision
- Copy of Ethics Committee opinion in the MS concerned where available.
- Additional information for special situations
- If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor
- Copy of authorisation for contained use or release of genetically modified organism (when applicable and available)
- Additional information according to member state requirements
- Subject related
- Informed consent form
- Subject information leaflet
- Arrangements of recruitment of subjects
- Protocol related
- Summary of the protocol in Hungarian language
- Peer review of the trial if available
- Signatures of the investigators
- Age of subjects exactly
- Permission of the director of the hospital
- Facilities and staff related
- Curriculum Vitae of the Hungarian principal investigators
- Facilities for the trial and information on the supporting staff
- IMP related
- Viral safety studies
- Examples of the label in Hungarian language
- Applicable authorisations to cover trials or products with special characteristics (if available) eg GMO, radiopharmaceuticals products
- TSE Certificate when applicable
- Declaration of GMP status of active biological substances
- Copy of the manufacturer authorization if the IMP is manufactured in the EU
- Declaration of the qualified person that the manufacturing site works in compliance with EU GMP (when applicable)
- Copy of the importer authorisation
- Analytical Certificate of IMP
- Sample in a quantity for a full analysis (beginning of the CT at the latest)
- Finance related
- Any insurance or infemnity to cover the liability of the sponsor
- Costs of clinical trials, division of costs between the hospital and investigator
- Compensation to subjects
- the letter of intention of the principal investigator
- the declaration of reception of the head of the service provider

to the NPI

NPI

send a copy of the complete application with an immediate effect

CPEC of HSC

the period of the special-ethical opinion giving procedure is sixty days

rejecting opinion

licensing opinion

the NPE does not license the trial

the NPE licenses the trial

the NPE sends the decision to

the National Health Insurance Office

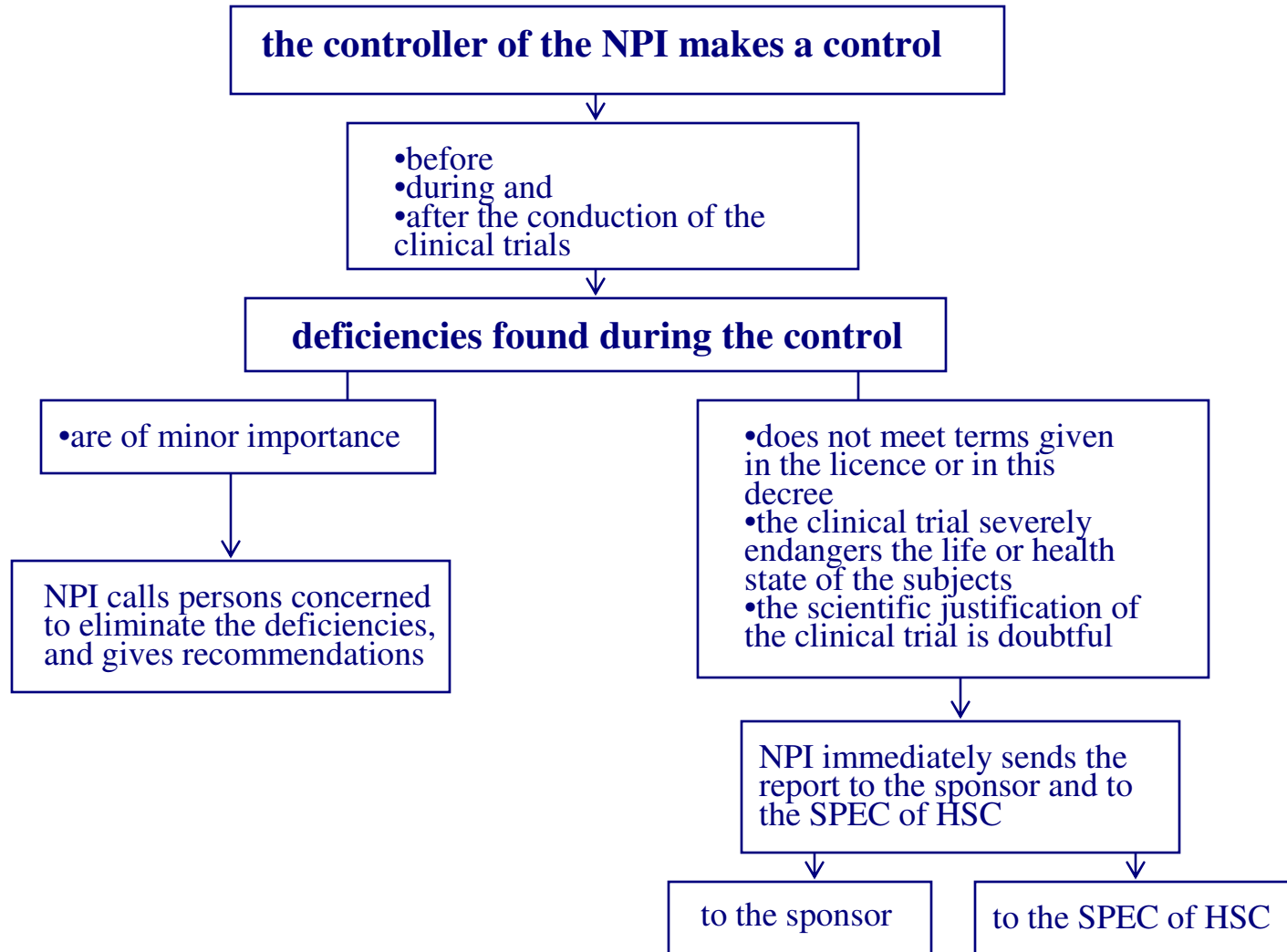
the CPEC of HSC

the competent IREC

the sponsor notifies

- the head of the health service provider conducting the clinical trial
- the competent IREC
- the principal investigator of the decision.


The control





Completion of trial

- The sponsor notifies the NPI on a data-sheet downloadable from the webpage of the EMEA within ninety days
- If the sponsor closes the clinical trial earlier than the planned date, he notifies the NPI of it within fifteen days
- The master file of the trial must be retained at least for five years after the completion of the trial



Asian Sponsors in the CEU Region and its potentials

- Takeda
- Sankyo
- Yamanouchi
- Eisai Fujisawa
- Taiho
- Daichi Asubio
- Kyowa
- Mitsubishi
- Nissui
- Otsuka
- Sumitomo



Ongoing Studies of Asian Sponsors in the CEU Region

- Studies registered with the FDA
- 1.14 % of the total number of clinical trials,
- Mainly European and US Sponsors,
- Sponsors acting through CRO's and not directly,
- Competitive patient enrolment,
- Growing tendency in the number of study sites and available Study Staff
- Very qualified and experienced research background