

Comments of the Czech Republic on the European Commission's concept paper submitted for public consultation to the "Revision of the "Clinical Trials Directive" 2001/20/EC.

Introduction:

Regulation of clinical trials in the Czech Republic falls under the responsibility of the State Institute for Drug Control (SUKL) since 1998 (previously it was under the remit of the Ministry of Health).

On average, SUKL assesses some 350 clinical trial applications (CTAs) per year. Its resources include 5 clinical trials assessors (FTE 3,25); 5 pharmaceutical assessors (FTE 3,25) and 3 preclinical assessors for toxicology part who are external experts (FTE approx. 0,6)

Directive 2001/20/EC, which should be implemented into national legislation of all EU Member States and forms a basis for assessment of all clinical trials, can be interpreted in different ways in some of its parts. The implication of this is that in practice there is no harmonized approach to assessment of clinical trials (CTs). However, the process of harmonization is being discussed for a long time in the European Union and coming to a conclusion is very difficult. The main criticism of the insufficiency of this harmonization was raised by European Federation of Pharmaceutical Industries and Associations (EFPIA) in documents assessing functionality of the Directive.

The Czech Republic supports the initiative and efforts to review Directive 2001/20/EC with the aim to adapt it to current requirements in drug development, regulation and harmonization of clinical trials assessment including protection of subjects' safety in clinical trials, high standard of investigational medicinal products (IMP), quality in relation to safety of clinical trial participants, retrieving validated data for future marketing authorization.

90% of all clinical trials conducted in the Czech Republic are multicentric, multinational clinical trials, only 10 % fall under national academic research and are conducted in one or more centres. Approximately 80 % of all clinical trials are commercial trials. Their sponsors are mainly pharmaceutical companies, only 20 % are either academic or professional societies, academic institutions or healthcare facilities from both the Czech Republic and other European countries. State Institute for Drug Control has been participating in the Voluntary Harmonisation Procedure (VHP) since its beginning and considers it as a useful tool for streamlining the clinical trials application assessment procedure. Building on our experience from this process we submit the following comments on the Concept Paper on Revision of the clinical trial Directive 2001/20/EC.

CONSULTATION TOPICS

1. COOPERATION IN ASSESSING AND FOLLOWING UP CLINICAL TRIAL APPLICATIONS (CTA) FOR CLINICAL TRIALS

The Czech Republic supports cooperation in assessment of clinical trials but wishes to point out that careful consideration must be given to particular characteristics of the approval procedure of each Member State.

From this point of view we appreciate the Voluntary harmonisation procedure (VHP) that fulfils the above mentioned criteria and its main aim is to reach harmonization - consensus between Member States.

1.1 Single submission with separate assessment

Consultation item no. 1:

„A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned.“

Do you agree with this appraisal? Please comment.

Single submission of all documentation through a single EU portal means that all documents will be available only in electronic format, which for the time being may not be optimal for all agencies.

If all documentation is planned to be in electronic version then a number of questions must be addressed, some of them may even require amendments to legislation, e.g.:

- 1) power of attorney - according to Czech legislation an original or certified copy must be submitted, which excludes electronic submission
- 2) clinical trial application supplemented with data applicable to each individual Member State (investigators, centres, number of planned subjects, ethics committee).
- 3) language issues – in addition to English also other language versions of some documentation must be submitted (Information for Patients/ Informed Consent Form; questionnaires, manuals etc.)
- 4) specific national requirements may include approval from other Authorities, in the Czech Republic it is the Ministry of Environment for medicinal products with genetically modified organism, State Office for Nuclear Safety for radiopharmaceuticals etc.

Additionally, it will be necessary to ensure backup of all documentation for all Member States, however, legal requirements for archiving differ across the Member States.

It is not clear whether single submission should apply only to National Competent Authorities or also Ethics Committees. Currently, Czech Ethic Committees accept only paper copies of documentation. How will this communication be managed, who will provide support for the committees including expenditures etc?

All technical provisions have to be established in detail since the beginning of this project to ensure success and avoid failure in future.

Consultation item no. 2:

“A separate assessment would insufficiently address the issue set out above: The difficulties created by independent assessments would remain.”

Do you agree with this appraisal? Please comment.

As regards separate assessment in the way it has been done till now we find it fully acceptable.

We would like also to mention time of assessment that is very often criticised by applicants. It should be noted that this time depends on quality of submitted documentation and quality of valid data. Sponsors frequently deliberately submit wrong, insufficient documentation which makes a clear hurdle for quick and easy assessment and approval. We believe that the problem with delay is not on the side of National Competent Authorities but on the contrary, the problem lays in insufficient quality of submitted data which are not in line with European guidelines and legislation.

1.2 Single submission with subsequent central assessment

Consultation item no. 3:

“A central assessment is not appropriate for clinical trials approval and would, as regards clinical trials, not be workable in practice...”

Do you agree with this appraisal? Please comment.

We agree with this appraisal and we strictly oppose central assessment for the following reasons:

1. It does not reflect particularities of individual Member States, e.g. the recommended procedure for antibiotics use, ATB policy, which differs among Member States and can lead to rise in ATB resistance.
2. If one Member State disagrees with the decision it will not have any chance to change it and that could have serious implications; this process is quite different from centralized authorisation of medicines - in the latter case a Member State has tools for regulation of access to the market - i.e. classification for use or method of reimbursement.
3. In the Czech Republic the deadline for study launch is limited to one year after approval. In case of a centralized approval this issue would have to be addressed, including control and potential implications in case of a long delay (updated data versus development of research etc.)
4. Finally, it could not apply to all investigational medicinal products (Investigational medicinal products), because some investigational medicinal products, such as genetically modified organism (GMO) and radiopharmaceuticals require a special procedure involving approval from other national institutions as mentioned above.

This way of assessment is not supported by not only by any member state, but also by Clinical Trials Facilitation Group (CTFG) which has mandate for harmonization.

This assessment should concern only competent/regulatory authorities but not Ethics Committees (EC) which are independent bodies. To coordinate the common approach is not feasible. The decision of ethics committees in the Czech Republic, both Multicentric Ethics Committees (MEC) and local ethics committees, is completely independent. They have their own standard operating procedures and they assess clinical trials especially from ethics point of view. In the Czech Republic there are 9 multicentric ethics committees assessing clinical trials in whole and local ethics committees which are responsible for assessment of investigators, facilities for conducting study on site.

1.3 Single submission with subsequent „coordinated assessment procedure“ (CAP)

1.3.1. Scope of the CAP

Consultation item no. 4: Is the above catalogue complete?

Consultation item no. 5: Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?

Coordinated assessment procedure is an interesting project which is similar to Voluntary harmonisation procedure (VHP), but not in all aspects. Basically, as in Voluntary harmonisation procedure (VHP-Version 2) there would be a rapporteur a co-rapporteur who would prepare assessment report for all concerned Member States. Each state could express its own grounds for non-acceptance (GNA) and the rapporteur should compile it in one version of grounds for non-acceptance. The timetable should be shorter. All this places more demands on all National Competent Authorities. Our resources were cut back at the beginning of this year and we would find it difficult to ensure sufficient resources for it.

The assessment and issuance of decision (approval /disapproval) by both National Competent Authority and Ethics Committee at the same time is unacceptable and impossible.

The deadline for assessment set at 60 days without exception is not acceptable. The time for assessment is laid down by Directive, but in the Czech Republic the assessment procedure is governed also by the Administrative Procedure Code, which is mandatory for all government institutions. In accordance with this law the applicant is entitled to sufficient time for response which often does not correspond with the 60 days' deadline. On the one hand this is a disadvantage for applicant as the period can be longer than 60 days (but the applicant can ask several times for clock-stop), but on the other hand this is an advantage, because the sponsor has enough time to reply to all requirements (otherwise a lot of studies would have to be rejected). The active time of assessment is 60 days, but as a whole it can be longer.

If there is no voluntary rapporteur and the rapporteur should be established, some Member States, including the Czech Republic, may face problems with limited resources. We fully support division of competences between National Competent Authorities and Ethics Committees. Duplication of work should be avoided as it saves time and money.

Within the CAP framework the following aspects are considered for assessment:

- a) Assessment of risk/benefit related to quality of IMP and labelling
- b) Ethical aspects - Information for Patient/Informed Consent Form, recruitment of trial subjects. In the Czech Republic the Information for Patient/Informed Consent Form is assessed by both national Competent Authority and Ethics Committee. A change to this model would require also a change in legislation.
- c) The choice of centre and investigator and its suitability is in the Ethics Committee competence. In the Czech Republic a responsible body for this is a local ethics committee, established in a concrete hospital or outpatient centre. There are nine independent Multicentric Ethics Committees and many local ethics committees, to harmonize their decision at one time would be impossible.

In summary, we agree that point a) should be in the competence of the CAP, while points b, c) are assessed by ethics committees and they cannot be included in the CAP.

In our opinion the important part of assessment is an assessment of the Protocol, Investigator's Brochure, Amendments from clinical point of view – suitability of protocol design, inclusion/exclusion criteria mainly from safety point of view, treatment, clinical visit and control assessment etc; preclinical assessment including toxicology, pharmacology, preclinical studies in animals etc.; benefit/risk for patients which is in competence of National Competent Authority. This part of assessment should be included in the CAP.

In the assessment due account should be taken of national particularities (for example choice of treatment as monotherapy, choice of antibiotics according to national policy, option between outpatient

treatment and hospitalization) where all National Competent Authorities should try to come to agreement, but not at any price; this applies mainly to safety of patients in clinical trials.

1.3.2. Disagreement with the assessment report

Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.

In case of disagreement with the assessment any Member State should have the option to “opt out” and the applicant would have to submit the clinical trial application through national procedure with required modifications.

Decision by simple majority is not acceptable, such decision cannot be considered legally binding and it would contradict our national legislation and national health policy. This experience is based on Voluntary harmonised procedure.

The third option, i.e. referral to the European Medicines Agency or the European Commission may be accepted only as a scientific advice or a recommendation.

1.3.3. Mandatory/optional use

Consultation item no. 7: Which of these three approaches is preferable? Please give your reasons.

CAP mandatory for all clinical trials - No, this approach seems unsuitable, at least for the beginning. The CAP will put more demands on National Competent Authorities, there will be need to gain more experience to evaluate the applications and decide how to proceed in practice, it might require some changes in legislation (as mentioned above, administrative procedure in case of Czech Republic, acceptance of electronic documentation, originals of documents, archiving).

CAP mandatory for all multinational clinical trials – this approach might be acceptable in future, if the following issues are addressed:

- introduction step by step with a transitional period
- readiness of National Competent Authorities both from scientific and technical point of view. We consider it as a demanding process for all National Competent Authorities, but the applicants would certainly benefit from this way of submission of clinical trial applications and obtaining approvals.

In the Czech Republic 85-90 % of clinical trial applications are multinational, multicentric studies and currently it would represent high administrative burden. It can be acceptable only if introduced stepwise and if sufficient time is given to the national Competent Authority to ensure personal and financial resources and technical support.

We consider the third option, where the **CAP is optional** - as the best solution. Member States could introduce it into practice stepwise, taking into account all circumstances mentioned above.

1.3.4. Tacit approval and timelines

Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.

Tacit approval – the Czech Act on Pharmaceuticals provides for this possibility, however, the Administrative Procedure Code does not and so it cannot be used in practice. In the Czech Republic, an administrative procedure has to be completed by a decision in writing before the clinical trial starts. Another problematic issue related to tacit approval concerns data in the European database, a need for written evidence for inspectors and audit of clinical trials. In addition, most healthcare facilities require a written approval from the National Competent Authority and Ethics Committee prior to commencement of a clinical trial.

In our opinion, the tacit approval might be feasible only for very simple clinical trials of phase IV when all investigational medicinal products are marketed in the Member States concerned, the trial is not placebo controlled and all investigational medicinal products are used according to Summary of Product's Characteristics.

We agree that a tacit approval is unacceptable for the CAP possibly with the exception of phase IV where all investigational medicinal products would be authorised in all Member States concerned.

Concerning timelines for the CAP, we consider the timeline of 60 days as minimal time for proper assessment, particularly when rapporteurs and co-rapporteurs have to compile all grounds for non-acceptance from participating states. Shortening this timeline would place additional burden on

national Competent Authorities and the documentation might not be assessed thoroughly, in particular from the safety point of view.

According to the Directive shorter timelines apply to phase IV (30 days) and we consider it as adequate. A shorter timeline for so called „low risk“ clinical trials we consider as risky for proper assessment and evaluation of risk/benefit for trial subjects.

2. BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS.

2.1. Consultation item no. 9:

“Rather than limiting the scope of the Clinical Trials Directive through a wider definition of ‘non-interventional trial’, it would be better to come up with harmonised and proportionate requirements which would apply to all clinical trials falling within the scope of the present Clinical Trials Directive.”

Do you agree with this appraisal? Please comment.

We agree with the definition of a “non-interventional trial” and we support the idea not to broaden the definition and thereby exclude more studies from the scope of the Clinical Trial Directive and decrease safety of clinical studies, which would fall out of regulation.

We suggest to define criteria for intervention more clearly. Further clarification is necessary for submission of these interventional studies under the Directive. For instance – how many ml of blood will be considered as nonstandard samples for testing, does it concern measurement of blood pressure in addition, questionnaires etc?

In our opinion, the academic studies should remain regulated and fall under the scope of the Directive, because of the following:

- new trends in development and research of modern therapy medicinal products
- necessity for other investigational medicinal products authorized or unauthorized considering the fact of patient safety and validity of all data

At the same time we do not see any need for labelling for marketed IMP and used in accordance with SPC.

2.1.2 Consultation item no. 10:

“Rather than limiting the scope of the Clinical Trials Directive, it would be better to come up with harmonised and proportionate requirements for clinical trials. These proportionate requirements would apply independently of the nature of the sponsor (‘commercial’ or ‘academic/non-commercial’).”

Do you agree with this appraisal? Please comment.

We agree with the comment (see paragraph above) and we also recommend to harmonize and simplify approach to academic sponsors for conducting clinical trials. Directive 2001/20/EC provides that the rules for academic sponsors should be simplified and this should be stipulated in a future guideline. The draft guideline has been discussed several times, but no rules have been issued yet. We would appreciate to discuss it further and to adopt a guideline setting clear simplified rules for academic sponsors (e.g. labelling, insurance etc.)

2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Consultation item no. 11:

“This approach would help to simplify, clarify, and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, risk-adapted set of rules.”

Do you agree with this appraisal? Please comment.

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?

We support harmonization process including harmonized rules for clinical trial applications, establishing rules (guidelines) and their implementation in legislation for clinical trials assessment, reporting Suspected Unexpected Serious Adverse Reactions (SUSARs), risk based approach.

The mentioned documents CT-1, CT-2 and CT-3 we consider as clarification for conducting clinical trials in the EU, however, we do not think that the documents simplify the whole process of assessment. For instance the clinical trial application form is comprehensive, but not easy to work with

both for applicants and National Competent Authorities; concerning safety reporting we do not see any advantage in DSUR versus ASR, and harmonized assessment of these documents we consider as impossible in the near future since there are no resources for it and responsibility for validity of these documents lies with the applicant.

Concerning safety reporting we miss reporting for non-investigational medicinal products (NIMP), which are used in studies and are authorized. If there is any adverse effect, data are available in the trial final report, but the marketing authorization holder does not have access to the data and cannot use it in further post marketing evaluation.

Currently, for all comparators, if authorized, sponsors report adverse drug reactions only if they are evaluated as SUSARs, but other (serious, but expected or non-serious and unexpected) should be reported to the EudraVigilance database, too.

2.3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Consultation item no. 13:

This combined approach would help to simplify, clarify, and streamline the rules for medicinal products used in the context of a clinical trial.

Do you agree with this appraisal? Please comment.

Definition of the investigational medicinal product and non-investigational medicinal product (IMP and NIMP) was discussed several times in the past. Until now, it has not been clarified unequivocally. We agree that an investigational medicinal product is a tested product and a comparator/placebo. A recently adopted guideline on IMP and NIMP (Guidance Documents Applying to Clinical Trials; Guidance on Investigational Medicinal Products (IMPs) and 'Non Investigational Medicinal Products' (NIMPs)(Rev. 1, March 2011) has established what products fall under NIMP and we fully agree that the guideline should be followed by all National Competent Authorities and sponsors. As regards amendments to the Directive on this topic, we suggest possibility for changes in labelling, e.g. no labelling for phase IV for low risks clinical trials. On the contrary, labelling for NIMP is not addressed at all and it may concern unauthorized NIMP the patient leaflet and labelling may be in a foreign language e.g. Japanese, what we see as confusing.

2.4. Insurance/indemnification

Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

For indemnification see point 2.1.

We agree that both proposals are acceptable.

first proposal: a need for insurance will be assessed according to risk (type of investigational medicinal product, number of interventions in clinical trial); academic sponsors and commercial sponsors for phase IV could cover indemnification only for quality failure, investigator has an insurance covered as a professional insurance in hospital where he is working as a physician

second proposal- is more complicated. It will lead in multinational studies to different approach and it will cause more problems for sponsors.

2.5. Single sponsor

Consultation item no. 15:

"In view of the above, option 1 may be preferable, provided that:

it is clarified that the 'responsibility' of the sponsor is without prejudice to the (national) rules for liability; and

it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised"

Do you agree with this appraisal? Please comment.

Basically, we agree with the Commission's appraisal. We find the first option (one sponsor) as more acceptable, because the full basic responsibility lies with one person and he may entrust e.g. a clinical research organisation (CRO) with other activities according to his decision.

The proposal for multiple sponsorship would be complicated and individual responsibilities would have to be clearly specified, since in the case of any claim it could cause a problem of „collective blame“ for breaking good clinical practice etc.

The possibility of multiple sponsorship would require a change of national legislation.

2.6. Emergency clinical trials

Consultation item no. 16:

“This could be a viable option in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts.”

Do you agree with this appraisal? Please comment.

The condition of patients enrolled in clinical trials under emergency conditions requires urgent action. There is no doubt that these studies are very necessary. Of course, they must be performed in compliance with the Helsinki Declaration and the Declaration on Human Rights and other related documents. Besides the above mentioned situations, also other problematic issues should be clarified and specified – e.g. use of placebo or Informed Consent under acute conditions.

In recent years, frequent discussions have been held on document of Patient Information and Informed Consent, but no significant changes have been achieved so far. Clear rules on what information to include in this document with regard to the health status of the patient vs. length of the text should be given. Experience has shown that harmonization of this document and proposals for improvement are needed. In practice, we have encountered cases such as: the sponsor submitted a document about the 6-8 pages to sign for patients with acute myocardial infarction when treatment was initiated already in the ambulance car. Similar examples were noted also in clinical trials with the following diagnosis: acute psychosis, dementia, stroke, etc., when patients were not incapacitated, they were not accompanied by their legal representatives and obtaining the patient's signature of such document is only self-justification situation where everyone involved in the assessment (the sponsor, regulatory agency, ethics committee, examiner) must know that signing such a document is not valid, even if they met the legal requirements and meet good clinical practice.

We suggest development of a guideline document for the Information for Patient/Informed Consent Form, which would clearly set the rules on not only the content but also the length and method of obtaining consent. (E.g. in acute myocardial infarction - verbal agreement after brief information recorded in the documentation and providing of signed consent after the patient is stabilized, it means two endorsements - one for acute state - up to 1 page and another after stabilization of the patient's medical condition, such recommendation for the harmonization of the documents is very desirable.

Note: Changes in the information for patient / informed consent form is desirable also for the way of inclusion of chronically ill patients for whom a newly developed therapy may be the only option, but they not meet the requirement of acute state. Such patient has no legal guardian, is not incapacitated, but is not able due to his medical condition to give informed consent. (e.g. a 3-7-page Information for Patient/Informed Consent Form document for patients with Alzheimer's disease, which should be very simple and short and should contain information given verbally by doctor).

3. ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Consultation item no. 17: Do you agree with this appraisal? Please comment.

Assessment of the situation in conducting clinical trials in third countries is a sensitive issue. In any case, we believe that it should strictly comply with the same rules as other clinical trials - the principles of good clinical practice to ensure patient safety, but also for the validity of the data. There should be set rules how to prove compliance with good clinical practice, especially in cases where the data obtained from clinical trials carried out in third countries will be used for marketing authorisation application. In these cases, we support to strengthen the monitoring / inspection activities. From our point of view, we find the only requirement – just only inclusion of such Clinical Trial in the EudraCT database as insufficient. If the data are to be used for the marketing authorisation of the product within the EU, there should not be sufficient to provide data from clinical trials carried out only in third countries (reason - e.g. interracial differences in pharmacokinetics, question of resistance to antibiotics, innate immunity due to a given environment, etc.). For these reasons part of clinical trials should always be conducted in Europe.

4. FIGURES AND DATA

Consultation item no. 18: Do you have any comments or additional quantifiable information apart from that set out in the annex to this document? If so, you are invited to submit them as part of this consultation exercise.

Annex

The Annex contains statistical data taken from the EudraCT database. This database according to the European Medicines Agency does not contain validated and therefore valid data. Some Member States do not fill the database continuously, and thus not all data are entered. When converting from EudraCT database version 7 to version 8 some already entered data were lost. Some countries enter into the database only the first version of the application form they receive, but do not provide any follow up.

Therefore, these figures should be taken only as approximate because they do not necessarily correspond to reality.