Comments from the Clinical Trial Department of State Institute for Drug Control (Regulatory Authority in the Czech Republic) on the assessment of the functioning of the"Clinical Trials Directive" 2001/20/EC

Introduction:
We are the only regulatory agency for human medicinal products in the Czech Republic. Since 1998 the assessment of clinical trials of medicinal human products have fallen in our agenda (previously it was in agenda of Ministry of Health for Czech Republic).
We assess 330 CTA (clinical trial application) in average per year.
Our resources: 6 clinical trial assessors (for this agenda approx. 4,25 work load; 5 pharmaceutical assessors - 3,25 work load and 3 preclinical assessors for toxicology part (approx. 0,6 work load).

Comments to separate points:

2.2. The Clinical Trials Directive

Consultation item No 1: Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of Clinical Trials Directive?

According to Directive the patient participating in clinical trial should not receive worse treatment than it has been established in clinical standard practice, but it can be sometimes a problem mainly concerning clinical trials performed by American sponsors , where are sometimes different rules for treatment. In this point, we believe in clear profit of Directive.
Some examples from our experience:

1. The tested IMP in clinical trial is surrogated by better efficient and safer medicinal product that is regularly used in the concrete indication in clinical practice, in another word the patient should be treated in CT by worse, obsolete treatment. It is unacceptable and it is not so rare example.
2. Repeatedly submitted insufficient pharmaceutical data, which without RA (regulatory agency) control should be used in patients.
   - stability data were not be submitted and after submission results concerning specification of IMP were very poor and unacceptable, there were increasing amount of impurities. Result: tested IMP is unstable and is not possible for patient's treatment.
   - Besides other shortages in pharmaceutical documentation-long term stability studies prove significant increase amounts of impurities. In addition there were submitted certificates of analysis which were not valide and shelf-life was expired.
   - IMP for intra venous use contained unknown particles "like cook oil" and sponsor insisted on use of the IMP. It is not acceptable.
3. Quite new IMP - first in human - sponsor suggests outpatient treatment - it is unacceptable

3. Multiple and divergent assessments of clinical trials

3.1. Despite the existence of the Clinical Directive countries have different requirements

It is caused by distinctions in local legislation – slightly different approach is logical because each country has its unique specifics that have to be respected.
Other important aspects are the differences in quality of nursing care, in standards of medical treatment, in guidelines between the countries. According to the Directive, the patient shouldn't get worse treatment than he would get normally without taking part in the trial. This

is a frequent problem in the case of US trials. Sponsor cannot impose rules for treatment that are against the rules/level/standards of the concrete country.

Some examples from our experience:

1) placebo arm in patients with severe depression on outpatient treatment
2) placebo in patients with severe stage of respiratory disease (COPD, asthma..), previous treatment is withdrawn during run-in phase at the beginning of the trial
3) patients with oncological disease treated preferably with study drug without proven effect, efficient therapy prohibited in the study – in case of study drug failure the patient starts efficient therapy with a big delay
4) health state assessment recommended for laboratory values much higher than in normal practice (for example: patient examined at PSA level higher than 10 micromoles per litre (Pfizer) but according to our guidelines the patient should be examined already at PSA level 4 micromoles per litre).

Solutions: Changes in the protocol can be made by the mean of local amendment or by Dear Doctor Letter if those changes are due to the differences of medical procedures or customs (for example: in the USA PPD Mantoux skin test is performed by general practitioner but in the Czech Republic the test can be performed and evaluated only by an expert from a pulmonary department or a centre specialised in tuberculosis. Therefore the USA model is not acceptable).

Clinical trials are assessed by both NCA and ethics committee

Logical and correct approach is justified by assuring the safety of the patient. Each institution assesses and comments clinical trial from a different point of view.
RA assess the expert aspects of the documents, is the only one to assess pharmaceutical data and the quality of the IMP. By analysing protocol and investigator's brochure it controls GCP compliance (no duplication of trials, no trials with worse treatment than normal practice, no excessive examinations, no excessive stress for patients) and legislation compliance.
Ethics committees assess ethical aspects of the trial, recommend or refuse sites and investigators, assess the realisation of the trial.
Although they control different things, they have a common aim – to assure the safety of the participants. Assessment of the protocol and investigator's brochure by both institutions is necessary.

RA (NCA) don't cooperate

The description of the situation is not accurate. The RAs communicate together more and more: through CTFG group and while consulting problematic trials. They interchange information and experience even though they don't have to share the same attitude. An important way of sharing information is the EudraCT database!
The cooperation is much more intensive than it used to be before adopting the Directive (there was hardly any cooperation) but at the same time it respects the particularities of the countries. We have active members in Clinical Trials Facilitation Group, CHMP - Safety working party, Committee for Advanced Therapies, CHMP Biologics Working Party, EudraCT Telematics Implementation Group (TIG), its Joint Operational Group (JOG) and Ad-hoc.

3.2

<u>Consultation item No 3</u>: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

<u>Quotations</u>: "The administrative costs for clinical trials, and thus clinical research, increase without added value. "

- The introduction of new IMP, especially product for advanced therapy requires more demanding and so more expensive assessment. Provisions for new steps in Pharmacovigilance reasonably require much more costs .The significant increase of sponsor costs falls into sponsor consideration of efectivity of carrying on clinical trials, better management of CT.
- Concerning academic trials - we try to help them, e.g. with preparation on documentation according to GCP, we prepare to adopt SUSAR reporting according to Directive instead of academic sponsor , we prepare workshops concerning requirements for submission CTA, give them updated information on legislative requirements (rights and duties of investigators and sponsors), we offer consultation and scientific advice free of charge and at the same time submission of CTA from academic sponsors are free of charge.

<u>Quotations</u>: "…separate assessment procedures of clinical trials by the various national competent authorities of the Member States concerned does not necessarily ensure the highest-possible standard of the assessment…"

- see comments 3.1; it is responsibility of each country how will ensure safety of subjects in CT

<u>Quotations:</u> "The inconsistent approach to the Clinical Trials Directive leads to longer delays for starting the clinical trial ("first patient in"), thus depriving patients of the results of clinical research…. "

- It is mainly fault of sponsors. In case that sponsor submit documentation of good quality meeting requirements of GCP, GMP and other relevant guidelines and safety of subjects will be insured , CT can be approved during much shorter period (max 60 days). But cutting time of assessment cannot be done to the prejudice of worse quality.

<u>Some examples from our experience</u>:

1. Poor preclinical data and sponsor wants to start a study.
2. Missing data from phase I, II studies, there are available only ongoing studies without any results and sponsor wants to start study phase III- big pivotal study without proven efficiency of IMP
3. Insufficient stability data, increasing amount of impurities in long term studies.
4. Incomprehensible, long Information Patient Sheet - e.g. 27 pages for patients with Alzheimer disease or IPS/ICF for patient with acute heart stroke, for paediatric use - there is not adequate information for age categories of children etc.

<u>Quotations:</u> "This, in turn, means that patients do not have access to new, innovative treatments, and the costs for the sponsor increase…."

- The information is unfitting and incorrect; the term " the newest and innovative" does not mean that this IMP are efficient and safe, these IMPs are in development and their efficiency is verified in long clinical process and additionally in post marketing use. The best option of treatment for patient is an available marketed medicinal product with proven efficacy and safety.

- As well in cases when there is not available alternative treatment it is not possible to confirm that tested IMP is the newest treatment, only future can give evidence about usefulness of IMP-benefit/risk for patient. There are a lot of examples of clinical trials which failed and CTs had to be interrupted and prematurely ended.

3.3 Options to address the issue as regards the assessment by NCAs

3.3.1. Reliance on voluntary cooperation of NCAs

The VHP process, whose implementation required many changes in NCA procedures and a lot of financial investment (Vitero system), is certainly beneficial. It shortened the assessment procedure (in our NCA less than 10 days from submission of a trial in VHP procedure to the issue of the final standpoint). It is acceptable for us because each NCA sends its comments. This process of submission has not be used much by sponsors till now.

3.3.2. Community-wide streamlining of NCA-authorisation process for clinical trials

Consultation item n°4: Can you give indications/quantifications/examples for the impactof each option? Which option is preferable? What practical/legal aspects would need tobe considered in further detail?

The centralized assessment performed by one body is unacceptable. It doesn't reflect unique specifics of individual countries. It cannot assure the quality of assessment, which is necessary for each state. It is impossible to take the responsibility over participants in the Czech Republic if the decision is made by another country.

Example from our experience:

- New tested antibiotic cannot be used as a medication of the first choice for a certain indication all over EU because member states have different condition of antibiotic resistance. In one country it can be used as a medication of first choice but in another it is not advisable because there are still other efficient antibiotics of common use.

General comments concerning this point:

- It is not acceptable to leave the decision of the type of submission on the sponsor.
- The actual system is working. Each important change in the procedure would mean big investment for RA (NCA) and EMEA, changes in legislation (not easy and fast), changes in database systems (EudraCT) and all connected systems.

3.4. Options to address the issue as regards the assessment by Ethics Committees

Consultation item n°5: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

- We disagree with "One-stop shop" for submission of assessment dossier. There is already functional system that is stabilized in the Czech Republic and is also continuing in harmonization of the activities of individual Ethics Committees, in their

improvement and in their proper functioning. In addition to the fact, that members of Ethics Committees are „groups of volunteers“, who work in Ethics Committees in excess of their normal work and mainly in their free time, sometimes with refundation of spared working time, but majority of the work of the Ethics Committee is not paid, further changes could be a possible cause of instability of actual system. Single ethics decision for the entire EU is unacceptable from the perspective of the historical development of individual countries, from differences in national traditions and customs. Local interests and the protection of subjects in each country would not be respected.

- We recommend better support for the activities of ethics committees, especially the financial support from the European Commission and EU funding to ensure better communication within the individual countries of the EU. Analogically to the expert working groups (e.g. CTFG ...) working group for members of the Ethics Committees would be suitable. There could be exchanged views, experience, harmonization of the assessment process within the EU in such working group (participation at the conferences of the European Forum of Ethics Committees is usually financially unavailable for representants of Ethics Committees).

4. INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE

<u>Consultation item n°6</u>: Is this an accurate description of the situation? Can you give other examples?

- Increase in number of Amendments concerning CT are not caused by requirements of regulatory agencies or ethics committees. It seems that most of these amendments have to be done to correct „quickly prepared Protocol. “ It is responsibility of sponsor who has to adapt Protocol according to new investigator’s experience from clinical practice.
- We support elaboration of harmonised guideline in which will be established clear rules for differentiation between substantial and nonsubstantial amendments. This guideline is to be in preparation by CTFG and Ad hoc group.
- In our opinion there is not possible to leave decision if it is SA or NSA on sponsors. There could be leak of essentials information, main changes of protocol e.g. changes in manufacturing process of MP, addition of other examinations during CT etc.
- Issuing the Directive as a Regulation does not solve anything. Directive cannot cover all problematic issues and thereto there are of course different possibilities of interpretation. On the other hand Directive has been implemented in European states and in spite of this not everyone considers it as mandatory. For instance: CTs phase IIa with following design has been approved by several states: new antidepressive drug, when only phase I had been done in healthy volunteers; in this phase IIa could be included outpatient patients with moderate or severe depression with presumption of removal previous therapy; further there is wash-out period only with placebo and follows randomization into 6 arms of which one is placebo arm, one is marketed comparator and others are with different doses of IMP. Time of treatment is 8 weeks – there will be done survey of recurrence of depression!? Implications can be serious: part of subject with severe depression will be without treatment with high risk of suicide for 11 weeks, further treatment with comparator is not assessed in final endpoint, efficiency is not proven - it means completely wrong unethical design which has been approved by some RAs. Directive has not been followed; as well GCP standards and the patient will be seriously threatened.

- These examples were more frequent before implementation Directive, now we believe that they are rare and the harmonized approach has been still improving (working group in scope of EMEA, worldwide cooperation in different organization etc.)
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<u>Consultation item n°7</u>: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?
<u>Consultation item n°8</u>: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case by-case basis?

- Complaints on increasing burden of administrative work concerning pharmacovigilance in CT are incorrect and misleading. Companies increase this administrative burden by wrong reporting – unsolicited reports, blinded reports, reports without identification, without assessment of relatedness to IMP. On the other hand sponsors report Urgent Safety Restriction without further important information, precautions for patients etc. and RA has to ask them for completing important fundamental information.
- In this moment there is not quite sufficiently available efficient EudraVigilance database, which should lead to better harmonised evaluation and removal of basic national databases. But the aim of EMEA and working groups is to complete operating system as soon as possible.
- Unequivocally the responsibility concerning process realisation of CT, reporting, assessment and ensuring safety precautions for subjects in CT is on sponsors.

5. REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

5.1. a 5.2

<u>Consultation item n°9</u>: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

- We agree with proposition for risk-differentiation in clinical trials. As example we present legislation duty for sponsor to ensure liability of indemnity for sponsor and investigator (covers insurance for patient) which is necessary also for phase IV. In these cases the IMPs are marketed products and are used according to SmPC, it means that involving subjects are treated according to clinical standard practise and would have been treated this way normally. These CTs are very often carried out by academic researchers or by physicians in clinical hospitals and insurance of indemnity … is often big problem and it is obstacle for carrying out these CTs (example: design - randomized comparative study with assessment of efficacy and safety of treatment A versus treatment B - both are marketed IMPs and are used in accordance with SPC). As well requirements for labelling of IMP marketed in country and used with accordance with SPC could be easier. The monitoring of this phase IV studies should be simple and should not demand financial burden for sponsor.
- The sponsor can deal with RA to adapt to practice for easier carrying out CT, especially for academic sponsors. On the other hand there is not possibility to leave academic research without control, but risk – differentiation should be considered.
- Concerning European guideline we support them, we participate in working groups and try to deal with problematic issues and harmonise them with others. This is the

question of rationale compromise. This is the reason why these guidelines cannot solve each problematic issue and cannot be very often quite clear, but the effort should be clarified them as most as possible. The other main problem is to respect these guidelines and accept the established rules. But keeping this will not be reach by Regulation.

Of course we support update these guidelines, because everything has been changing and developing. But we see the necessity keeping guidelines by each RA in EU.

- The claim about obstacles from RA for patients we have commented -see above and we only repeat that this statement is untruly and exaggerated by sponsors and these sponsor's real aim is not to do correct CT , but to achieve easy MA with low cost. The speed is not guarantee either for quality or safety. The responsibility of each RA and EC is to ensure safety of patients in CT realized in concrete country. The speed does not mean right benefit/risk for patient.
- The statement of the document about "decreasing competitiveness European CT" proves clearly and corresponds with commercial interests of manufacturer and does not reflect interests of subjects safety, with guarantee of quality of IMP, quality of carrying out CT. It is unacceptable and should not be taken in mind to correct Directive, guidelines this way. The document only confirms our opinion that safety of treatment, quality of IMP, safety of subjects in CT is not very often the priority of pharmaceutical sponsors and RAs have to regulate the commercial interest of pharmaceutical companies.

6. ADAPTATION TO PECULIARITIES IN TRIAL PARTICIPANTS AND TRIAL DESIGN

<u>Consultation item n°14</u>: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

- Changes are being prepared – in the new version no.8 of EudraCT database (starting in June 2010). All information about paediatric studies should be available, including data from PIP trials taking place in third countries.
- Paediatric patients need to be protected more as they represent a vulnerable population. We don't agree with the statement that Directive hinders development of paediatric medicines and treatments. The Directive only assures protection of the children, which is really necessary according to the experience (new drug with no proven efficiency in adults should not be administered to children, no placebo should be used in trials where there is an efficient therapy that (as comparator), excessive baseless blood collections, no respect for the minimalisation of pain where it could be prevented – usually pharmacokinetics – all that without any remuneration, but remuneration cannot be incentive for participation.

<u>Consultation item n°15</u>: Should this issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experience?

- In the field of emergency medicine, careful and strict requirements on safety of the participants are also absolutely necessary. The situation is analogical to what was said for children – placebo is unacceptable in those cases, when an efficient treatment is available and the patient, if randomised to placebo arm, would be in a high risk of an impairment or low probability of recovering.

7 - ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES ("GCP") IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

We have only general comments concerning the last chapter of the document. The issue of involving third countries in the research is delicate. We promote the idea of third countries taking part in the clinical trials, but we don't agree with the proposal of displacing the research mainly or entirely to the third countries.
We don't share the opinion that thanks to the realisation of clinical trials in third countries local people would receive treatment that wouldn't be accessible for them under normal circumstances. It is very often true, but we don't think this approach is justified. We find it unethical to offer therapy in cases where the treatment needs to be long-term (for example in chronic diseases, AIDS etc.) but couldn't be continued after the end of the study.
The second problematic issue is the compliance with GCP standards. Certainly it would be appropriate to give more attention to the inspections in this area. But on the other hand would there be enough staff to assure the inspections? Would there be enough financial resources to execute the inspections? The research should be global. If a medical product is designed to be used all over the world, the pre-authorisation research should be done also in different places of the world. The efficacy data can be influenced by many circumstances - genetics, ethics, national customs..., what should be taken into account already at the stage of IMP development.

FINAL CONCLUSION:

The publication of the Directive 2001/20/EC, its implementation into national legislations and especially its introduction in practice brought significant improvement in the scope of clinical trials. It helped most of all in terms of a better quality of assessments, progressive harmonisation of assessments by NCA and ethics committees, strengthening of the cooperation and mutual communication of the RAs. It also reinforced inspections in the area of realisation of the clinical trials. All these lead finally to the possibility of ensuring bigger safety of the participants in the trials, higher quality of tested products and higher validity of data.
There is always something that can be improved. Therefore it is advisable to update the Directive according to new knowledge and experience. Adjustments of problematic points have to be made as well (for example: clear distinction between substantial and non-substantial amendments, simpler rules for academic research that doesn't lead to the authorisation of the IMP or to changes in the authorisation, simpler rules for interventional trials of phase IV – like insurance, labelling…).
Contrary to the opinions presented in the document, we don't agree with the implementation of centralised procedure in clinical trials which would be upon the choice of the sponsor. We are against massive displacement of clinical trials to the third countries as an optimal solution of actual situation. We don't promote one common standpoint of ethics committees which would be valid for whole EU.
We suggest next reinforcement of the cooperation of RAs, but of course the reinforcement of the cooperation of ethics committees is necessary to develop and improve. Other important issue is the education of all staff participating in the realisation of a clinical trial, like investigators, investigational staff, members of the ethics committees.
We encourage the continuation of meetings of specialised working party CTFG, oriented on concrete problems, where specialist in a concrete field would meet. This year such a meeting was organised for oncology trials and it would be beneficial to organise similar meetings for paediatric trials, one e.g. concerning ICF for members of ethics committees and a meeting

focused on adaptive designs. Each meeting should have the form of a workshop with concrete examples and discussion with effort to harmonise approach. We entirely agree with reviewing of the conditions for academic and purely non-commercial research and try to do them easier, but safe.