Separate document - **comments from pharmaceutical assessors from the Czech Republic RA (Regulatory Authority) see below**:

Directive 2001/20/EC in practice – advantages and disadvantages

Czech comments:

Topic 2:

- The final decision of the Regulatory Authorities are usually similar, however, the RAs have a different requirements/questions.
  - even the 2 assessors of the same RA would never have the same requirements/questions. It depends on the education/specialization of each assessor who assess the clinical trial documentation
  - final approval depends on the fact whether the company is able to provide more information or perform a required study/measurement. It does not mean that the clinical trial could be approved earlier without these additional data.
- The RAs do not cooperate during the assessment of the clinical trial.
  - in case of major objections, the RAs communicate, however, this is only consultation not a mandatory decision.

Topic 3:

- The administrative costs for clinical trials, and thus clinical research, increase without added value.
  - the safety of the patients have priority over science (we cannot accept new drug product if it is evident that e.g. degradation after short time storage period is too high and sponsor does not care about this situation, even if there is no other medication for the disease)
- Longer delays for starting the clinical trial

The companies very often do not provide sufficient amount of data. Data abundance leads to the longer time necessary to the assessment.

More often, the provided data are insufficient. There are some examples:

- The company provided stability data of the drug substance/drug product only for one batch and only after 3 months of the storage. They asked for the 24 months shelf-life.
- The company changes completely the manufacturing process of the drug substance and does not prove the comparability of the drug substance from the previous and the new manufacturing process. In this case it is not possible to use data generated with the drug substance from the previous manufacturing process, for example elucidation of structure, impurity profile, stability data etc. Further, in case that the comparability would not be proved, the data generated from such clinical trial would not be possible to use during the MAA.
- Proposed acceptance criteria for some impurities are not toxicologically justified.
- The in-use stability data is completely missing.
- The manufacturing licences for investigational medicinal products are not provided or are invalid.
- The Qualified Person Declaration does not contain all manufacturers outside of the EU.
- It is necessary to follow requirements set down in the PhEur and/or in some of the Agency guidelines (relating to DP in CT). The serious disease is not the reason to compromise the quality of the drug product.
- There are discrepancies in the IMPD - information provided on one page is in contradiction with information on other page. For example, one of the by-products is

not impurity because it has same potency as the drug substance. But on other page is written that this by-product shows a potential toxicity.

- The repeated assessment of the documents.
  - it is very often the fault of the companies. They can provide only simplified IMPD, however, they provide full IMPD without the highlighting the differences with the IMPD which was already assessed. Also, the companies provide documents which are not necessary or data which are not required. They have to be read and the assessment is prolonged.
  - only answers to the RA questions/comments to the submitted IMPD should be provided or sponsor's conformity statement with previous documentation approved by the RA. The corrected full IMPD is not required.

Topic 4:

- A common process of assessment should be introduced in the member states.
  - voluntary cooperation of the RA during the assessment. It would be possible, but the decision should not be mandatory for the RAs. In our opinion, this would lead to the prolongation of the assessment time since there would be necessary time for the RAs communication and communication between RAs and the sponsor.
  - assessment on the basis of decentralized procedures (DCP)/mutual recognition procedures (MRP). We would not agreed with this approach because some of the member states do not assess the clinical trials at all and there is not assurance of the comprehensive assessment (medical assessment, risk assessment, quality data assessment etc.) of the clinical trial in some of the member states. Further, this procedure would prolong the time of the assessment as well as the previous procedure.
  - centralised assessment in the European Medicinal Agency (the Agency). In case all the member states could express its opinion as in case of centralised procedures (CP), this would be good approach. But a new working group(s) consisting of experts experienced in CTA assessment should be established within the Agency just for CTA assessment. We do not agree that this assessment would be done as a Scientific Advice. In addition, this process would cause problems to small companies or academia especially at the beginning of the development phase when quite often consultations/scientific advices are provided by regulatory authorities. These meeting should not be taken place at the national level but in the Agency to be more relevant for the applicant.

In each case, the common procedure would lead to the prolongation of assessment period in comparison to national terms because additional time for communication between individual authorities is needed. And also, more assessors are then needed.
Harmonisation of the assessment among different assessors is supported but there are doubts that it can be done by legislation changes. The process of harmonisation at the scientific level has started by preparation of scientific guidelines (e.g. Guideline on Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials, Guideline on Chemical and Pharmaceutical Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials, and Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products).

The common approach for CTA assessment within EU would be possible only if the relevant legal framework is identical. Currently, there are some specific aspects where the requirements differ. One of these differences is classification of borderline products. There are important differences in a national legislation and therefore one product can fulfil a

definition of medicinal product in one member state but it would be a medicinal device or something else (such as cosmetics, tissue and cells, food supplement, ...) in the other.

Topic 6:

- Different explication of the Substantial Amendments (SA)
  - some of the companies' expectations are not realistic. For example, when the company provides the stability data which show trends in increase of the impurities or decrease of the drug substance content, we would like to see the following time points in order to assess the prolongation of the shelf-life. It often depends on the type of the medicinal product and the type of the implemented change. We assess the providing SA case-by-case.

Topic 9:

- The requirements are not proportional to the potential risks.
  - each IMPD is assessed after the assessment of potential risks, seriousness/frequency of occurrence of the disease, patients population etc. However, appropriate quality and safety of the IMP have to be demonstrated irrespective of an indication or development phase. No patient should be exposed to the redundant risk.