Member States with respect to the communication of safety information to the ethics committees. The representatives of ethics committees also supported this view.

The guidelines on safety reporting, whilst considered by many observers to be very good, are perhaps those with the most diverse implementation at the national level. A major driver for the diversity of, or non-compliance with, these guidelines is the burden created by having to submit extensive multiple reports to various parties. These parties take varied, mostly uncoordinated, steps to avoid the overload of their resources by placing limitations on the extent, nature or timing of the information to be supplied.

3.5.1. Suspected unexpected serious adverse reactions (SUSARs)

Directive 2001/20/EC requires expedited submission of all suspected unexpected serious adverse reactions to the NCAs and to the ethics committees. However, these do not have the resources to review and evaluate their content, resulting in too much information being sent to too many recipients.

The commercial sponsors highlighted the following practical difficulties that contribute towards duplication of cases, under-reporting and over-reporting, and inconsistent report formats:

- Diverse safety definitions (within or between companies and regulators) for:
  - important medical events
  - expectedness
  - seriousness.
- Diversity of safety-reporting requirements placed on them by legislation, by NCAs and by ethics committees, including:
  - electronic and/or paper submission of 'local' and 'foreign' SUSARs
  - cases originating in third countries
  - cases from different trials with the same IMP
  - unblinded versus blinded case reporting.
- Difficulties with reconciling clinical-trial and post-authorisation reporting requirements where the IMP also has a marketing authorisation, in relation to:
  - requirements for products with a marketing authorisation, dependent on where authorisation is granted and whether the trial is conducted using the product within the SmPC
  - cases arising from spontaneous reporting or other sources outside of clinical trials.

The ethics committee representatives pointed out that receiving too much information in a non-concise form often leads to data overload and the loss of relevant safety signals, which can ultimately undermine the role of the ethics committees in patient-safety protection.

There were calls for simplification and streamlining of safety reporting, with regard to:

- requirements for marketed products used in clinical trials
- annual reporting in clinical trials
- electronic reporting and use of the EudraVigilance database

submission (what and when) of unblinded or blinded cases to the NCAs, ethics committees and investigators.

3.5.2. Annual safety reports (ASRs)

It was stressed that the science of analysis of safety signals from clinical trials is an area where much progress still has to be made, and that the models used post authorisation will not necessarily work in the pre-authorisation stage. In this context, the relative purpose and value of the ASRs and of expedited reporting for the evaluation of the overall safety profile of a medicinal product examined in the clinical trial were questioned.

3.5.3. EudraVigilance

It was generally felt that electronic reporting is a step forward. However, EudraVigilance training is still very much industry-orientated, and non-commercial sponsors requested a lower training fee and promotion of pharmacovigilance training for non-commercial sponsors.

Commercial sponsors recommended that EudraVigilance should be used to capture all SUSARs and SSARs (suspected serious adverse reactions), in order to optimise safety-analysis and signal-detection capabilities.

CROs do not have the possibility of registering independently with the EudraVigilance database, which adds to the administrative burden of providing a quality safety service for clinical-trial sponsors and marketing-authorisation holders.

NCAs would welcome a system that allowed them to have a complete overview of patient safety, rather than having to deal on a case-by-case basis with the individual major events that are very rare.

3.5.4. Summary of recommendations in relation to safety-reporting in clinical trials

Proposed measures within the current legal framework:

- Harmonisation of safety definitions and of guidelines for classification of reactions such as expectedness, significant medical event and relatedness.
- Enable CROs to register and report directly using EudraVigilance.
- Annual safety reports should be IMP- rather than clinical trial-specific, so that clear safety issues can be identified and risk-benefit ratio evaluated, whilst reducing administrative burdens.
- Agreement of report formats and their content.

Proposed measures within the context of a new/revised legal framework:

- Electronic reporting of SUSARs (per IMP, not per clinical trial) should be made mandatory, preferably with one point of data entry in a single, unified format.
- EudraVigilance database should be a common directory/repository for all SUSARs and provide an efficient tool for identification and generation of safety signals.
- EudraVigilance should capture SSARs in addition to SUSARs.
- Work-sharing across the NCAs and ethics committees for evaluation of SUSARs and of ASRs.

- Grant access to EudraVigilance for ethics committees.
- Establish a legal basis for the establishment and maintenance of the EudraVigilance Medicinal Product Dictionary.
- Clear reporting rules to ethics committees, NCAs and investigators, with particular emphasis on streamlining information sent to ethics committees and investigators and on providing them with an accurate overview of the safety status of the study population.
- Reporting to the investigators should be reduced to submission of periodic reports and safety analyses.

3.6. Transparency

There is increasing transparency in the fields of development and of regulation of medicines. Assessment reports of marketing-authorisation applications are publicly available, whether the outcome is positive or negative, or the application is withdrawn. Consequently, information on clinical trials forming part of a marketing authorisation is publicly available. On the other hand, there is no comprehensive legal tool to ensure public dissemination of the conduct and outcome of studies that are not part of a marketing-authorisation submission, with the notable recent exception of paediatric trials. Globally, clinical-trial registers are an increasing feature of the publication of information; initiatives include those of the WHO, the International Standard Randomised Controlled Trial Register and International Federation of Pharmaceutical Manufacturers' Associations (IFPMA), those of the FDA, and other regional registers, including those developed by individual pharmaceutical companies. The requirements of the International Committee of Medical Journal Editors (ICMJE) have been one factor driving public registration of clinical trials, including non-commercial clinical trials.

The development to date of the EudraCT and EudraVigilance databases was welcomed, but public access to the information contained, and in some cases the legal framework for this, needs to go further.

3.6.1. Legal framework for public access to clinical-trial information

The EU clinical-trials database, EudraCT, was initially a database intended for the use of NCAs, the European Commission and the EMEA. Directive 2001/20/EC prevents access of other parties to the database. However, the 2004 revision of the pharmaceutical legislation opened up the possibility of publishing some data from EudraCT on some ongoing or completed clinical trials. This information should be included in the public database of authorised medicinal products (EudraPharm), which is under development. The Paediatric Regulation goes even further, by requiring public availability of EudraCT data for all clinical trials in children, and by requiring the inclusion in EudraCT and publication of the results of these trials — including trials conducted in third counties.

Nevertheless, data on ongoing trials conducted in adults prior to a marketing-authorisation application remains confidential. During the conference, patients and healthcare professionals asked for more information on those trials, which represent a substantial and very important part of the clinical trials conducted. Representatives of NCAs also supported the concept of a comprehensive European clinical-trial register.

3.6.2. Factors motivating greater transparency

Transparency is necessary to ensure that the best information is provided to healthcare professionals and patients about the safe and effective use of medicines. Patients have a right to information about medicines and their development, so its provision is a process in which patients and society in general are intimately involved.

Furthermore, increased transparency is important in preventing unnecessary repetition of research — a key goal identified in the paediatric legislation and elsewhere. Transparency helps to ensure the ethical and scientific quality of clinical trials, both ongoing and completed. The dissemination of knowledge within the scientific community is of major importance in driving further, better research.

Commercial sponsors are concerned with protecting their intellectual property and maintaining a reasonable competitive advantage for their novel development programmes. However, non-commercial sponsors and patients, in particular, pointed out that knowledge is a major driver of innovation and that transparency contributes to knowledge. In the view of patients, the additional impetus and gain offered by increased transparency would drive research further and significantly outweigh the disadvantages perceived by the commercial sector.

Transparency of information on ongoing clinical trials may also lead to a wider range of therapeutic options and facilitate clinical trials for diseases where safe and effective treatment is absent or requires significant improvement.

Non-commercial sponsors pointed out that they need a good public register of clinical trials in order to be able to publish the results in medical journals, and EudraCT should provide this for the EU.

The NCAs called for new legislation to support a clinical-trial register in the EU, based on EudraCT. Patients, non-commercial sponsors and ethics committees called for more transparency on ongoing clinical trials and their outcome.

Non-commercial sponsors proposed that there should be a repository for clinical-trial data allowing re-analyses and meta-analyses, to optimise the scientific use of data collected.

The current evolution in patient care — towards a patient/healthcare-professional partnership in the choice of treatment and for early access to new treatment — reinforces the need for wide transparency in the field of clinical trials. Public trust in clinical trials is an important factor in supporting patients' willingness to participate in trials, and conference attendees stated that increased transparency would be a key step in building and maintaining this trust.

3.6.3. Next steps

As a first step, transparency could be improved by completing the implementation of publication of data from EudraCT, in the context of the current legal framework. The Commission is expected to publish a guideline soon for this purpose. Activities in this area are currently ongoing, with work being done on defining the information to be published and on developing the necessary IT tools to give access to this information.

The GCP IWG also called for more transparency on the activities and outcomes of GCP inspection.

A second necessary step would be to revise the current legal framework to include provisions for further transparency of all clinical trials and of the results of those trials.

3.6.4. Summary of recommendations in relation to transparency

Proposed measures within the current legal framework:

- Complete the implementation of the current legislation as a matter of priority (paediatric legislation and inclusion of clinical trials in the context of Article 57 of Regulation (EC) No 726/2004).
- Ensure that publication of clinical-trials information fulfils the data requirements of the ICMJE and is compatible with other international registers and portals.

Proposed measures in the context of a new/revised legal framework:

- Reinforce legislation at EU level for the registration and publication of information on all ongoing clinical trials, and, when completed, on their results — i.e. a comprehensive EU clinical-trials register, compatible with other international clinical-trial registries and portals.
- Establish a clear legal basis, at EU level, for greater transparency on inspections of clinical trials.
- Provide a clear legal basis for publication of clinical-trial-related information contained in EudraVigilance.
- Develop a repository for clinical-trial data allowing re-analyses and meta-analyses, to optimise the scientific use of data collected.

3.7. Inspections

The process of inspection has become an important tool for examining GCP compliance. All stakeholders had a positive view of inspections carried out on behalf of the Community, with the results being recognised by all Member States, coordinated, where applicable, by the EMEA.

Speakers consistently acknowledged enforcement of GCP standards for clinical-trial conduct as a major contribution of Directive 2001/20/EC. Compliance with GCP provides assurance of the credibility of results, and of the rights, safety and well-being of patients.

3.7.1. Inspection processes

The GCP IWG welcomed the legal framework for the system and scope of GCP inspections, implementation of this system, appointment of inspectors by the Member States, and mutual recognition of the inspection results, which the Directive has provided. Furthermore, the group reported finalisation of the inspection procedures for GCP inspections conducted in the context of the centralised procedure, and these have been published. The common GCP-inspection guidance required by Directive 2005/28/EC is under preparation, and should be finalised and transmitted to the European Commission for publication in the coming year.

The inspectors considered the GCP IWG to be an efficient platform for exchanging information, for training, and for developing consensus and procedures.

There is an ongoing process for in-situ training of inspectors through joint inspections that involve different Member State inspectorates on each occasion. There are also training courses organised by the GCP IWG.

The GCP IWG would like to see a better process for the distribution/sharing of inspection reports between Member States.

Members of the ethics committees felt that their involvement in both the inspection decision-making process and the actual conduct of the inspection could be increased, in particular considering their central role in the approval of study sites; ethics committees are often informed about inspections only after they have been completed, and sometimes not at all.

The CRO associations felt that the GCP inspections are not sufficiently harmonised; specifically, they felt that routine inspections of ongoing clinical-trial activities in the Member States deserve better planning and coordination amongst the inspectorates. They pointed out that the same clinical trials are inspected in different Member States without apparent coordination or communication between the inspectorates involved. Similarly, the same CRO may be subjected to multiple unconnected inspections in different Member States.

An improved process for consultation of the GCP IWG by interested parties would be welcomed by the CROs, and the GCP IWG foresaw improving access to advice for interested parties.

3.7.2. Information on inspections

The inspectors need better access to searching and reporting of information in EudraCT. They want to improve the usefulness of the EudraCT database as a directory of inspections and their findings, in order to harmonise inspection planning and to coordinate their collective inspection plans with the national Member State programmes.

Members of the GCP IWG are currently preparing a common schema for categorisation of GCP-inspection findings, in order to make the analysis of the inspection outcomes more efficient and to facilitate their publication. There is also an ongoing discussion regarding the management of confidentiality aspects, and the degree to which the reports should be available to the public — a matter restricted by the legal framework at present.

Although the current legal system specifies that the inspection report shall be sent to the sponsor, to other Member States, to ethics committees and to the EMEA, no recommendation is given on their availability to other recipients, e.g. inspectees, marketing-authorisation holders or applicants.

3.7.3. Inspections and mutual-recognition agreements

The industry representatives expressed a critical view regarding the current lack of mutual recognition of inspection results between the EU and the FDA, which leads to duplication of inspections and, ultimately, to inefficient use of resources.

3.7.4. Summary of recommendations in relation to inspections

Proposed measures within the current legal framework:

- Improve coordination across the EU of inspections of ongoing clinical trials and clinical-trial facilities (e.g. CROs, laboratories).

- Complete the GCP-inspection guidance foreseen by Directive 2005/28/EC.
- Analyse and publish anonymised inspection findings.
- Increase collaboration among EU and US inspectors, and mutual recognition of inspection results, to avoid duplication of inspections.
- Involve ethics committees in the inspection process, from initiation to sharing of results.
- Complete the scheme for classification of GCP-inspection findings and their publication.
- Promote inspector training.
- Reduce the inspection fee for non-commercial trials.

Proposed measures within the context of a new/revised legal framework:

- Include inspectees and marketing-authorisation holders in the definition of recipients of the inspection report.
- Improve the legal framework for publication of inspection findings and reports.

3.8. Patients' perspective

The Co-chair of the Patients' and Consumers' Working Party (PCWP) was invited to participate in the conference and to present the patients' perspective. Other representatives of patients' organisations participated as delegates to the meeting and contributed to the discussions.

On the positive side, patients' representatives stated that the Clinical Trials Directive had provided procedures that are more transparent, and provided a greater level of protection of individuals. This has been achieved through clear requirements for the protection of subjects, the establishment and operation of ethics committees, and respect of GCP. Persons incapable of giving legal consent have been taken into consideration, as have children.

By increasing the level of consistency in the conduct of clinical trials and their compliance with GCP principles, the Directive has also had a positive influence on independent (non-commercial) clinical research. Despite some remaining concerns about increased administrative burden, the Directive has improved the rigour with which non-commercial clinical trials are conducted.

High quality in research should combine the best ethical conduct with the highest achievable scientific standard. The patients' representatives underlined how all these achievements demonstrate EU excellence in the scientific and ethical conduct of clinical trials — an excellence that must remain a reference for the world.

Concerns were raised in the following areas:

heterogeneous implementation of the Directive, in particular in the context of ethics committees

lack of transparency of clinical-trial information

informed consent.

3.8.1. Ethics committees

The composition of ethics committees varies greatly across Member States, and sometimes within the same country, potentially leading to a disharmonised approach to clinical research. Not all EU countries foresee the participation of patients as members of ethics committees, and where this is specified, the level of involvement foreseen varies. Patients can offer a valuable contribution to the ethics committees in different ways, whether acting as members or being consulted as experts on a case-by-case basis.

Despite the time limits set out in the Directive, patients' representatives noted that considerable delays and disharmony still exist across Member States.

The patients also expressed concern that evaluation of clinical-trial applications by some ethics committees or NCAs is performed rather quickly, leading to a form of competition and the favouring of some of them by applicants, and raising concerns about the adequacy of the assessment.

One area where patients can make a valuable contribution as members of ethics committees is in the thorough and independent review of the written informed consent, the quality and comprehensibility of which varies greatly across the EU at the moment.

3.8.2. Treatment after the trial

Patients are not always guaranteed cost-free continuation of a successful treatment at the end of a trial.

3.8.3. Transparency of clinical-trials data

The EudraCT database is not accessible to the general public. The system, by allowing the sharing of information between competent authorities, does help to promote the safety of research, but it does not allow the public/patients to find a clinical trial to participate in, nor to obtain information on the main outcomes of performed trials. Greater transparency of information on ongoing and terminated clinical trials, including their outcome (of both authorised and new investigational medicinal products), has been requested.

Patients' representatives also noted that patients who are subjects in clinical trials are not consistently informed of the outcome of the clinical trial in which they have directly participated.

3.8.4. Other issues noted

It was also noted that research in some fields, such as paediatric oncology, is still very difficult. Solutions are needed to help non-commercial researchers in this field overcome staffing and financing difficulties.

Patients' representatives supported the call from non-commercial researchers for a solution to the problem of a single sponsor through some form of co-sponsorship.

As far as definitions are concerned, patients agreed that the regulation of non-interventional clinical trials should be reconsidered. Non-interventional clinical trials, as currently defined, do not fall within the scope of the legislation. This leads to a double standard for clinical research, a lack of harmonisation in non-observational research amongst different countries, and differences in the applicable ethical requirements.

3.8.5. Summary of recommendations made by patients' representatives

(See also patients' representatives' contributions to other sections.)

Proposed measures within the current legal framework:

- Guidelines on informed consent should be developed to ensure consistent, high-quality documents throughout the EU.
- The functioning of ethics committees should be harmonised across the EU.
- Patients should be more involved in the work of ethics committees and their contributions should be harmonised.
- Infrastructural resources for non-commercial research should be improved.
- Better provision should be made for the continued availability of a successful treatment to trial subjects after the end of a trial.
- Ensure that subjects who have participated in a trial are properly informed of its outcome.

Proposed measures within the context of a new/revised legal framework:

- There is a need for consistent and continuous provision of information to patients before, during and after finalisation of a clinical trial. As part of this, final clinical-trial outcomes should be systematically made public as soon as possible.
- A minimum time should be set for the evaluation of clinical-trial applications by ethics committees.
- Non-interventional trials should be brought within the scope of the legislation.

3.9. Clinical trials in developing countries

The conduct of clinical trials in developing countries is faced with difficulties not usually encountered in the EU: the burden placed on very limited healthcare systems by poverty-related diseases is enormous.

The spread of tuberculosis and of HIV infection is a serious issue, and malaria continues to cause millions of deaths every year. Only 1% of newly developed drugs are designed for the treatment of tropical diseases. Although these are neglected diseases, 'orphan drug' status may not be available to some of them. The weakness of health systems makes it difficult to put in place adequate preventive measures, and it can be difficult to afford new technologies. Despite these difficulties, some results have been achieved in the treatment of leprosy, trachoma and oncocercosis. Some interventions, such as 'kangaroo care' (placing premature babies in strict contact with their parents), are truly innovative.

Opinion number 17 of the European Group on Ethics has proposed some important principles, stressing that research activities in third countries cannot be assimilated to an economic activity subject to market rules, and that trials in third countries cannot be avoided for reasons of convenience.

The development of EU and ICH requirements needs to foresee greater influence of developing countries in the research and development of medicinal products. The EU and ICH need to take into consideration the differences in ethics, consent and cultural

acceptance of clinical trials in developing countries. Increased capacity-building for research in developing countries, and the development of trial sites and of training, have to be considered as priorities in the context of achieving access to treatment.

There have been several initiatives to help focus minds and improve international progress towards meeting the UN Millennium Development Goals, such as the G8 and the Mexico Ministerial commitments relating to health research on neglected diseases.

The European & Developing Countries Clinical Trials Partnership (EDCTP) was set up in The Hague & Cape Town in 2003. EDCTP involves 14 EU Member States, plus Switzerland and Norway and some African countries, and uses as its basis Article 169 of the EU Treaty. EDCTP has the overall goal of reducing poverty in developing countries by improving the health of their populations. It aims to develop new clinical interventions to fight HIV/AIDS, malaria and tuberculosis. EDCTP requires North/South country partnerships, the achievement of better European research integration, and a sustainable partnership with African countries.

A decision of the Council has made it possible to provide €200 million in European funding for EDCTP, and Member States are supposed to contribute another €200 million.

After a difficult start between 2003 and 2005, major efforts have been undertaken since 2006 to improve the performance of EDCTP. The European Commission has supported the request for a cost-neutral extension of the EDCTP grant to 2010. Member States must match the European Commission contribution to EDCTP-funded projects — a requirement reflected in the most recent calls and in direct contributions. It must be kept in mind that co-funding is one of the instruments for achieving integration of national programmes, and so far, only part of the funding has been obtained from the Member States and from third parties.

Amongst the challenges EDCTP has to face is that more funding will only be provided under the Seventh Framework Programme (FP7) for research if certain conditions are met first by 2010. These conditions are:

- attainment of better results from field activities in Africa and in integrating national programmes
- generation of a real joint programme between member states
- attract attention and mobilisation of the EU pharmaceutical industry
- ministers to renew EDCTP 'vows' and to provide real fresh funds
- establishment of ownership of the EDCTP by African countries (political, scientific and institutional)
- development of specific EDCTP procedures in the context of intellectual property rights and for ethical review.

Input should be sought from pharmaceutical companies that are involved in clinical trials in poor countries and from the WHO/Special Programme for Research and Training in Tropical Diseases (TDR). Their support should be obtained for establishing the public availability of information contained in clinical-trial registries.

The EMEA and Commission should reinforce their activities in assisting EDCTP, and the synergies between EU institutions, DG RTD/DEV/SANCO and the EMEA should be part of this.

Article 58 of Regulation (EC) No 726/2004, which foresees that the EMEA gives scientific advice to the WHO, could be used for provision of advice to EDCTP. The CHMP guideline on scientific opinions for products marketed outside the European Union should include explicit provisions on GCP and on ethical conformity of trials performed outside the European Union, and this should be addressed in the summary opinions published on the EMEA website.

Furthermore, Recital 8 of Directive 2003/63/EC requires a systematic test of the GCP and ethical equivalence for all clinical trials performed outside the European Union. The evaluation process must fully address these aspects when there is no mutual-recognition agreement with the country where the trials have taken place.

Therefore, European public assessment reports (EPARs) relating to marketing-authorisation applications assessed in the EU should include a clear description and account of the assessment of the ethical standards achieved during the conduct of clinical trials.

Any review of Directives 2001/20/EC and 2005/28/EC should evaluate and consolidate provisions for the protection of clinical-trial subjects, both within and outside the EU. Emphasis needs to be placed on the avoidance of 'clinical-trial dumping', i.e. conduct of clinical trials in third countries because it is seen as easier to perform the trials in those countries that do not have an adequate regulatory framework. This could lead to inadequate GCP standards, generation of invalid or unethical data, and threats to the rights, safety and well-being of patients. There is a need for careful monitoring of GCP compliance of trials conducted in third countries. GCP inspection in these areas should be increased in order to assure a higher level of compliance.

3.9.1. Summary of recommendations in relation to clinical trials in developing countries

Proposed measures within the current legal framework:

- Monitor the potential of 'clinical-trial dumping' in third countries, particularly those trials included in marketing-authorisation applications to the EU.
- Review CHMP guideline 5579/04 on the scientific opinion for products marketed outside the European Union.
- Enforce the GCP and ethical equivalence testing of clinical trials conducted in third countries, as required under Directive 2003/63/EC (8), and describe their assessment in the EPAR.
- Further increase EU GCP inspections in developing countries.
- The European Commission and Member States should:

  promote adaptation of ICH/EU GCP principles via WHO

  help develop capacity for ethical review and oversight of clinical trials in developing countries

  support capacity-building in developing countries — for ethical review, trial review, authorisation and inspection

  increase support to non-commercial clinical research, i.e. EDCTP.

Proposed measures within the context of a new/revised legal framework:

- Improve provisions in the clinical-trial legislation for the protection of trial participants in third countries.
- Open Article 58 of Regulation (EC) No 726/2004 to include provision of assistance to EDCTP.
- Open EU clinical-trial registers (e.g. EudraCT) to clinical trials conducted in developing countries.

3.10. Final discussion and perspectives for the future

In the later sessions, senior representatives of different sectors involved were invited to describe how they see the future developing in response to the issues raised during the conference. They focused mainly on areas for improvement — the challenge now is to move forward and take steps to resolve outstanding issues. The high-level points are summarised below.

3.10.1. Commercial sponsors/CROs

The representatives of commercial sponsors and CROs emphasised the need for Europe to remain a key location for the conduct of clinical research. The EU legislation and national implementing legislation should be reviewed in order to achieve real and effective harmonisation, transparency and consistency in the approval and conduct of clinical trials in the EU. Numerous improvements can be achieved by addressing the guidelines and practices within the current legislation, by foreseeing some changes to the Directives themselves or via a regulation for certain aspects.

These developments should set out to provide:

(within the current legal framework)

clear provisions and definitions

reduced flexibility of interpretation and implementation

single point of entry for submission of clinical-trial-authorisation applications, and harmonised data requirements for all Member States

centralised safety reporting via EudraVigilance

streamlined review processes (of NCAs and of central and local ethics committees)

clearly defined roles and responsibilities of ethics committees and NCAs;

(through an amended legal framework)

a system of mutual recognition of NCA assessments

enhanced role of the CTFG (based on the experiences with MRFG/CMD(h))

new optional procedure with one assessment (a single approval per study would be particularly suitable for multinational studies)

new legislation that is able to capture, prospectively, the complexity of developing new clinical trials in the field of advanced therapies.

3.10.2. Non-commercial sponsors

The non-commercial sponsors had expressed the greatest difficulties with the clinical-trial legislation, but also took a wide view of the potential scope of new legislation. Better as well as more clinical research should be the aim. More attention should be given in this process to other existing sets of European legislation, such as the Council of Europe Convention on Human Rights and Biomedicine and its additional protocols.

A new legal framework should:

- be a single and comprehensive piece of legislation covering all clinical research (A regulation would be preferred to a directive.)
- protect participants according to the risk associated to the category of study, not to the study's commercial or non-commercial objective
- include provision for a single assessment by one competent authority
- include provision for accreditation of ethics committees
- provide clear guidance on the respective roles and harmonised interactions of ethics committees and NCAs
- promote trust, transparency and optimal use of data, through open registration, reporting and data repositories.

3.10.3. Ethics committees

The ethics committee representatives were particularly concerned to achieve greater communication and access to information on clinical trials, and to have more support for their infrastructures and for training of their members. They emphasised that there should be no centralisation of the ethics opinion at EU level. The goal is to develop the protection of human subjects in all types of clinical research.

The major issues that need to be addressed are:

- clearer separation of duties of NCAs and ethics committees
- better communication between ethics committees themselves and with NCAs, and improved access to information for ethics committees
- change of the safety-reporting requirements of the Directive
- access to EudraCT and EudraVigilance for ethics committees
- training and education: case-studies database
- development of harmonised documents
- quality-management and self-evaluation of ethics committees
- greater involvement of lay persons
- provisions for clinical trials in emergency situations, in particular in relation to informed consent.

3.10.4. National competent authorities

The NCAs emphasised that, compared to the situation prevailing prior to 2004, considerable harmonisation has already been achieved. Rather than changing the

Directive at this stage, they suggested that an incremental approach would offer a greater chance of success. Clinical trials have an essential role in bringing innovative medicines as quickly as possible to patients. Cohesion, simplification and transparency are keys for the success of European research.

Their main points related to:

- harmonisation and reinforcement of collaboration between NCAs (CTA requirements, scientific assessment, etc.)
- simplification and clarification (the roles of NCAs and ethics committees, SUSAR reporting and assessment, electronic submission, etc.)
- improve data-sharing between Member States and data-analysis via appropriate information systems as prerequisites
- prompt and accurate population of EudraCT
- transparency
- information-exchange with stakeholders (CTFG); support and training for non-commercial sponsors
- availability of recommendations and Q&A on a dedicated website
- risk-based approach
- creation of infrastructures within Member States to increase the number of clinical trials conducted in the EU.

3.10.5. Patients

Patients asked that a key objective be to maintain the EU as a global reference for excellence in science and ethics in clinical trials, both within and outside the EU.

They recommended:

- greater patient involvement in ethics committees
- informed-consent guidelines for EU, in terms of both content and structure
- free-of-charge treatment for patients at the end of a trial
- public access to information on trials in EudraCT
- clinical-trial results must be available within a defined timeline (e.g. one year)
- minimum review period for ethics committees when they give an opinion
- non-interventional clinical trials to be included in the legislation.

3.10.6. European Commission DG Research

The representative of the Directorate-General for Research addressed activities in support of clinical research in the EU.

They identified the need for, and actions supporting, active and continuous coordination:

- with DG Enterprise and Industry and EMEA on the legislative/regulatory issues
- with non-commercial sponsors for key issues such as the definition of 'non-commercial clinical trial' and 'sponsorship'

- coordination with ethics committees, regulators, competent authorities and research organisations.

In addition, specific funding is envisaged for:

- SMEs involved in research projects
- non-commercial clinical trials
- planning to extend the coverage provided by the funding from the 7th Framework Programme to the entire clinical trials spectrum, within the 'non-commercial' sector

  the fields of off-patent medicines for children and medicinal product safety, as a priority.

They stressed that data obtained from non-commercial clinical trials should be acceptable for marketing-authorisation purposes.

3.11. Perspectives for the future (Closing comments from DG Enterprise)

Mme Georgette Lalis of the European Commission Directorate-General for Enterprise and Industry concluded the conference. Mme Lalis presented DG Enterprise's immediate understanding and impressions of the main themes raised during the conference and its thoughts on how the issues may now be taken forward.

The Commission indicated the need:

- to bring more coherence and harmonisation to the system (and this will not happen only through guidelines)
- to get a common interpretation of the legal aspects, including definitions
- to make procedures more streamlined
- to ensure more transparency on the operation of the system
- to check whether requirements for non-commercial trials take due account of their specificities.

The Commission indicated the need for continued reflection on these issues and on whether changes to the existing legal framework are required, and assured that extensive consultation on these matters would take place.

The Commission stated that the issues raised in the conference are of crucial importance in ensuring that:

- EU patients get the best medicines
- EU industry is more competitive at international level
- EU pharmaceuticals-research community develops.

Integral text of Mme Lalis's closing remarks to the meeting

European Commission-EMEA Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future

I am very pleased to have the opportunity to make some closing remarks at the end of this important initiative, the Conference on the Operation of the Clinical Trials Directive, and to present some perspectives for the future.

This initiative, commended by the European Commission to the EMEA, is particularly important as it represents the first action to assess the impact of the operation of Directive 2001/20/EC. In this context, the Commission wanted to involve all the parties that work in the field, at practical level, with the implementation of this legislation in the European Union: the national competent authorities, the ethics committees, the sponsors of commercial and non-commercial clinical trials, researchers, patients and others interested in the area.

You are all aware that since the start of the implementation of Directive 2001/20/EC, the pharmaceutical industry, as well as academic researchers, have expressed strong concerns about the implementation of this legislation due to the different ways Member States were applying it in concrete terms.

At its meeting of 5 December 2006, the Pharmaceutical Committee endorsed a report on the activities of the 'Ad hoc group for the implementation of Directive 2001/20/EC', which confirmed that the experiences linked to the implementation of the legislation varied from Member State to Member State. This clearly showed that, unfortunately, some of the obstacles as regards the administrative burden and differences in implementation were not overcome yet.

Therefore, the purpose of today's conference is to take stock of the existing situation, involving all major stakeholders, with a view to evaluating whether further work on the implementation would help us solve existing problems and whether a revision of the Directive is necessary.

The high level of participation, the number and quality of speakers, and the great interest raised by this initiative show the importance of performing this exercise.

I have myself followed the entire meeting and I am very pleased with the extensive discussions that have taken place during the conference, which now comes to an end.

Before going into the concrete points I want to make, I would like to express, on behalf of the European Commission, our gratitude to the EMEA for the organisation of this event, and to thank Thomas Lönngren and, more specifically, Fergus Sweeney and all those closely involved with the organisation of the Conference, for the excellent work done. I also want to thank the Programme Committee members and all the speakers and participants for their involvement, support and collaboration on this initiative. A word of thanks also to my colleague from the Commission, Rui Santos Ivo, responsible for the Clinical Trials Directive, as well as to our colleagues from other countries who came to participate in our reflections and share their views.

The first remark I have to make is that this Conference recognised the importance of maintaining the principles enshrined in the legislation for the conduct of clinical research in the European Union, which I want to mention again:

- protect patients

- ensure high-quality research in the EU
- promote a favourable research environment.

The question for us is how to make the system more efficient so that it will deliver on public health and avoid unnecessary burden to sponsors.

I will try to regroup the different issues brought forward today as follows.

Implementation of the Directive

Although criticised by most speakers, the EU legislation has contributed to more harmonised practices and to the respect of timeframes. It has brought significant improvement to the quality of research and the protection of patients.

I consider that the situation is better now than before, even if not optimal.

Differences persist, due to diverging interpretation and national implementation of the texts, that create increased administrative burden and, possibly, more costs. It seems that there are cases of gold plating, which often happen when we regulate through directives. An issue, therefore, for future reflection could be whether we need to change the form of the legal instrument into a regulation.

It is clear to us that competent authorities indicate that they are happy with the current system and are ready to work on rationalising outstanding issues through existing channels. They oppose a centralised system and want to maintain national competences.

The pharmaceutical industry and mainly academic sponsors do not seem to share this opinion; the two have massively asked for changes in the regulatory framework, with a different degree of intensity. In between, the ethics committees want more visibility and the possibility to exercise better their responsibilities.

Finally, as far as patient organisations are concerned, I was happy to hear that they consider that this legislation has brought benefits for the quality of research and for the treatment of patients.

As Commission services, we are very keen to see the system run smoothly, so that diverging implementation does not affect negatively the conduct of clinical trials and, eventually, lead to the shift of its conduct outside the EU.

Different solutions have been proposed on how to improve the system, and we will carefully consider them. It is clear that some issues can be addressed immediately; others need changes in the legislative framework. For the time being, I have to say the main fora where discussion and immediate solutions can be tackled are the Working Groups on Clinical Trials — the one chaired by the Commission to develop guidance and the group set up by the Member States.

Multinational clinical trials

The problem of divergence in national practices seems to impact more on multi-centre trials.

In the recent 'first-in-human' trials discussion, the need for more intensive cooperation and exchange of information was recognised for this type of trial.

Therefore, clearly, we need to address the issue, because in the future we will have more and more trials, either because of the nature of drugs or because of the diseases we want to treat.

Again, some ideas for introducing more harmonisation were presented today, like:

- a mutual-recognition system for clinical trials
- or a central coordination mechanism
- or even a centralised assessment mechanism, based on EMEA's networking system.

A lot of discussion today was around the 'centralised' mechanism. I need to clarify that this is in reality a network of Member State experts and agencies.

Safety-monitoring of clinical trials

At the heart of the legislation lies the safety of participants in clinical trials.

However, we see from different interventions that national procedures addressing this concern may lead, or have led, to unnecessary hurdles that, at the end of the day, could amount to less safety.

The suggestion was strongly made by different participants that it is appropriate or even necessary to streamline the reporting system of safety information, and use available resources and tools in better analysing this information.

Ideas came up for establishing a single entry point for the collection and analysis of safety information. This needs further discussion, and most probably can occur without changes in the legislation.

Non-commercial clinical trials

All clinical trials involving a medicinal product fall under the Directive. The nature of the sponsor is not relevant for that purpose.

Non-commercial sponsors have, since the start, considered the implementation of the Directive to be a hurdle to research.

We have listened very carefully to the issues presented by the research community, and I am happy to see that it does not request a specific framework.

After all, the safety of participants in a clinical trial is paramount, and should be the same whatever the nature of the sponsor. It also struck me that most of the proposals made by the research community concern also commercial sponsors. Therefore, it is more the functioning of the Directive itself that is at stake.

I leave the issue of financing out of the present discussion because it is not directly linked to the Directive.

Finally, on this topic, we will also look carefully again into the draft guideline on non-commercial trials.

Clinical trials in third countries

This issue is at the heart of Vice-President G. Verheugen, together with the issue of possible exports of substandard drugs and counterfeits.

We have a series of ongoing regulatory dialogues with countries like India, China and Russia, where the need for common standards in clinical trials is already being addressed.

In addition, the Commission is working with WHO towards supporting capacity-building in developing countries.

We will look carefully into new ways of addressing common ethical principles and GCP standards with developing countries, also by considering the different cooperation tools

available. We will also have to check whether the provisions of the EU legislation are adequately implemented in this field.

Last, but not least:

Transparency and access to information on clinical trials

Important suggestions have been made today concerning the availability of information on clinical trials. We know how important this information is to both patients and the health professionals, who have a potential interest in ongoing or completed trials. Also to sponsors and investigators, for them to contribute to the development of further research, to ensure that better trials are designed, requiring fewer patients and avoiding unnecessary duplication.

The Commission wants to contribute effectively to fulfil these needs, and a guideline with the view of making available information on clinical trials through the EudraPharm database is being finalised. With the same purpose, the recent Paediatric Regulation introduces clear requirements for the Agency to make available information on paediatric trials, including the results of trials conducted in the EU and in third countries.

For me, this will be one of the issues that will draw the spotlights of public opinion in the near future, as clinical trials come more and more under public scrutiny. There is an issue of public trust and confidence in drug development.

Conclusions and moving forward

Today we have listened carefully to all the different views on the issues that need to be addressed to tackle certain existing problems, and have heard about new options that may be considered for the future. Speakers also have mapped in detail many aspects from different angles. As the Commission, we have perhaps better understood the functioning of the system, where unnecessary complexities exist, and where simplification is required and possible.

Today's discussion has been very rich for us, and has shown the importance of conducting this exercise and listening to all parties involved with the conduct of clinical trials, especially the experts in the field. It is more than clear to me that we need: to bring more coherence and harmonisation in the system — and this cannot happen only through guidelines; to get a common interpretation of the legal aspects, including definitions; to streamline better the procedures; to ensure more transparency on the operation of the system; and to check whether requirements on non-commercial trials take due account of their specificities.

The discussions today have demonstrated the necessity to continue the reflection on the future of the clinical-trials legislation in Europe. I cannot tell you today what the outcome of this reflection will be. In terms of procedure, the EMEA will prepare a report of this meeting, reflecting the contributions to this conference and the outcome of the discussions. This will certainly constitute an important element to identify all the relevant issues, both those which can be easily tackled and those which will require deeper considerations.

We will discuss the issues with our Commissioner and deepen our internal reflection.

If the decision is made to bring changes to the existing legal framework, be assured that we will extensively consult on the different options that we will consider — not only with medicines agencies, but also with all stakeholders concerned. In parallel, we will also perform a public consultation through the Commission website. Moreover, of course, if we

are to propose changes, we will have to undergo a thorough impact-assessment in line with the rules of our better-regulation principles.

The issue we discussed today is of crucial importance if we want to ensure that:

- EU patients get the best medicines
- EU industry is more competitive at international level
- EU research community in pharmaceuticals develops.

Thank you.

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