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

Conference held on 3 October 2007 at the EMEA, London

— REPORT ON THE CONFERENCE —

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Abbreviations list

Abbreviation	Definition
ASR	Annual safety report
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract research organisation
CTA	Clinical trial application
CTFG	Clinical Trials Facilitation Group
DG DEV	Directorate-General Development, European Commission
DG RTD	Directorate-General for Research, European Commission
DG SANCO	Directorate-General for Health and Consumer Affairs, European Commission
EDCTP	European and Developing Countries Clinical Trials Partnership
EEA	European Economic Area
EMEA	European Medicines Agency
ESF-EMRC	European Science Foundation – European Medical Research Councils
EU	European Union
EVCTM	EudraVigilance Clinical Trial Module
FP7	Seventh Framework Programme
GCP	Good clinical practice
GCP IWG	Good Clinical Practice Inspectors Working Group
GDP	Good distribution practice
GMDP	Good manufacturing and distribution practice
GMDP IWG	Good Manufacturing and Distribution Practice Inspectors Working Group
GMP	Good manufacturing practice
HMA	Heads of Medicines Agencies
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IFPMA	International Federation of Pharmaceutical Manufacturers' Associations

Abbreviation	Definition
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
ISRCTN	International Standard Randomised Controlled Trial Number
MRFG	Mutual Recognition Facilitation Group *Now called 'Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human', or CMD(h)*
NCA	National competent authority
PCWP	Patients' and Consumers' Working Party
QP	Qualified person
QWP	Quality Working Party
SMEs	Small and medium-sized enterprises
SmPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reactions
WHO	World Health Organization
WHO/TDR	World Health Organization/Special Programme for Research and Training in Tropical Diseases

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1. EXECUTIVE SUMMARY

At the request of the European Commission, the European Medicines Agency (EMEA) organised a conference on the implementation in the European Union (EU) of legislation on clinical trials of medicinal products.

The objective of the conference, which involved a wide range of interested parties, was to provide an overview of the experience to date with the existing legislation — by providing an analysis of what aspects work well and what aspects do not — and to establish recommendations for future improvement.

It was recognised by conference participants that the legislation on clinical trials has introduced a common legal framework and a legal basis for compliance with good clinical practice (GCP), and has improved the protection of individuals through procedures for ethical approval of clinical trials in the EU.

Participants stressed the importance of maintaining the general principles of protecting patients, facilitating high-quality research and promoting a favourable research environment in the European Union, whilst ensuring that the clinical-trials system is efficient and that sponsors do not bear any unnecessary burden.

It was acknowledged that, in some cases, problems that have been encountered appeared to be a consequence of different interpretations and different implementation in the national legislation of the Member States.

Conference participants felt that some of the difficulties experienced could be resolved within the current legal framework, by providing additional clarification, guidance and harmonisation, whereas others would need to be addressed through proposed changes to the legislation.

It was suggested that, since any change to the legislation is likely to take some time, work should begin immediately on tackling issues that can be resolved without such a change. The main areas in which efforts should be focused are multinational clinical trials, safety reporting and monitoring, non-commercial sponsorships/trials, CTA dossier and process, and IMP-related issues.

Other areas that will require specific attention include increased transparency and availability of information on clinical trials, and the application of ethical principles and GCP standards in developing countries.

While it is clear that further discussion amongst all interested parties is required to provide the best-possible legislative environment for clinical trials in the EU, the conference generated a very useful dialogue on the most pressing issues and put forward a series of proposals that can be taken as the starting point for immediate as well as long-term improvements, and for future action by the European Commission.

2. BACKGROUND

The European Commission requested the European Medicines Agency (EMEA) to organise a conference, involving all interested parties, on the state of play with the implementation of the legislation related to clinical trials of medicinal products. This topic is of major importance for the protection of patients, for clinical research, for competitiveness of the pharmaceutical industry and for European research. The objectives of the conference were to provide an overview of the experience to date with the operation of Directives 2001/20/EC and 2005/28/EC and their implementing texts, to describe their impact, to specify problems encountered and to offer recommendations for the future.

The clinical trials legislation is relatively recent. Directive 2001/20/EC of the European Parliament and of the Council established specific provisions regarding the conduct of clinical trials on medicinal products for human use in the European Union, in order to ensure a common set of rules to be implemented by Member States. Commission Directive 2005/28/EC laid down principles and detailed guidelines on good clinical practice for clinical trials of investigational medicinal products for human use, as well as requirements for authorisation of the manufacture or importation of such products. Commission Directive 2003/94/EC on the principles and guidelines of good manufacturing practice extended the application of these principles to the use of investigational medicinal products in clinical trials.

The national competent authorities (NCAs), in conjunction with the ethics committees, are responsible, in each Member State, for the oversight of clinical trials and their conduct in the EU. The NCAs review and authorise clinical trials, review amendments and safety reports, conduct inspections and authorise manufacturing sites in their territories.

Subsequent to the entry into force of Directive 2001/20/EC, the European Commission established an 'Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use'. The group is composed of representatives of the NCAs and the EMEA, and is chaired by the European Commission DG Enterprise and Industry. The objective of the group has been to develop the implementing measures and the guidance documents required by Directive 2001/20/EC and its implementing legislation, in order to ensure a harmonised approach amongst Member States to the conduct of clinical trials in the European Union, and to ensure that the requirements established in the Directive are observed.

At its meeting of 5 December 2006, the Pharmaceutical Committee endorsed a report on the activities of the Ad hoc group. This report confirms that experience with implementation of the legislation varies between Member States and, further, that it is not yet possible to fully assess the impact of some of the guidance prepared. Nevertheless, it appears that some of the obstacles posed by differences in implementation and by administrative burden have not yet been overcome.

Following the implementation of Directive 2001/20 /EC in May 2004, the EU Heads of Medicines Agencies (HMA) established the Clinical Trials Facilitation Group (CTFG) to coordinate the implementation of the Clinical Trials Directive across the Member States at an operational level and further improve harmonisation of regulatory requirements relating to clinical trials across the Community. Its mandate is published on the HMA website (http://www.hma.eu). The clinical trial units of the EEA national competent authorities (NCAs), the European Commission and the EMEA are represented on the group. The

CTFG's objectives include supporting the efforts of the European medicines network with regard to public health by fostering a harmonised regulatory environment for clinical trials conducted in the EEA. CTFG is working to establish and improve communication channels within the European medicines network, and to develop and promote harmonised processes and procedures relating to clinical trials within the scope of the duties of the NCAs. It acts as a forum for discussion and agreement on common principles and processes to be applied throughout the network, and operates to improve harmonisation of the administrative procedures and assessment decisions for clinical trials across the NCAs. This work includes sharing of scientific assessment, harmonisation of processes and decisions, participation in the development of information systems, communication and cooperation with other working groups, including the Commission's Ad hoc working group, telematics implementation groups and the scientific working parties of the Community.

The EMEA works with the CTFG and with other technical groups on the management of two databases: the clinical trials database (EudraCT) and the EudraVigilance Clinical Trial Module (EVCTM — a specific module for the electronic reporting of suspected unexpected serious adverse reactions (SUSARs) by sponsors during clinical trials). The EMEA also convenes and chairs the Good Clinical Practice and Good Manufacturing and Distribution Practice Inspectors Working Groups, which contribute towards preparing implementing guidance for the Directives on good manufacturing practice (GMP), good distribution practice (GDP) and good clinical practice (GCP) inspections.

The Committee for Medicinal Products for Human Use (CHMP), through its Quality Working Party, developed a guideline on the 'Requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004)' in order to harmonise the requirements. The CHMP, through its Safety and Efficacy Working Parties and in collaboration with clinical trials experts representing the CTFG, has recently developed a scientific guidance document, 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)', which is important to the conduct of first-in-human clinical trials in the EU.

The conference held on 3 October 2007 was a stocktaking exercise, involving all major interested parties, with a view to evaluating whether further work on the implementation of the regulatory framework could resolve existing problems or whether a revision of the current legislation is necessary.

Representatives of commercial sponsors, non-commercial sponsors, ethics committees, national competent authorities, patients and investigators were invited to provide their views on the practical implementation of the regulatory framework, and to identify practical difficulties.

The conference was attended by 267 delegates representing national competent authorities, ethics committees, commercial and non-commercial sponsors, contract research organisations, patients' organisations, the European Commission and the EMEA. Six journalists were also present. (Attendees are listed in Annex B.)

A programme committee was established to prepare the conference, to identify topics and to identify representatives of the various interested parties who would present their respective positions. Each organisation invited to nominate delegates was also invited to prepare a written submission. These are available on the EMEA website. (See Annex C.)

Interested parties were requested to reflect upon and focus their presentations on four key questions:

- What aspects of the current legislative framework work well?
- What does not work well?
- What can be remedied within the current legal framework?
- What should a new legal framework look like?

A further topic in the programme related to clinical trials in third countries.

Sections of the report

This report is divided into sections on key issues arising from the conference presentations:

- Scope of the legislation and definitions
- Clinical-trial application and review process
- IMP and GMP issues
- Ethics committees
- Safety reporting in clinical trials
- Transparency
- Inspections
- Patients' perspective
- Clinical trials in developing countries

At the end of each of these sections, the recommendations are summarised as bullet points. Section 3.10 contains the summary of perspectives for the future as seen by the stakeholder groups. Section 3.11 contains the closing comments from the European Commission's DG Enterprise.

These are the key recommendations made by one or more of the stakeholder groups during the meeting. In some cases, they may be contradictory or may not represent the views of all present, since the purpose of the meeting was to listen to all positions, not to establish consensus at this point in time.

The slides of all presentations given during the conference, plus other documents relating to the conference, are available through the 'Conferences & Events' section of the EMEA website:

http://www.emea.europa.eu/meetings/conference.htm

Summary of the conference programme

Session 1

Opening statement, objectives, and background.

Session 2

Scope of legislation.

Definitions.

Clinical trial authorisation and IMP dossier:

- to ethics committee
- to competent authority.

IMP-related issues (definitions, labelling, GMP, etc.).

Ethics committee structures and processes.

Competent authority processes.

Roles of ethics committees and NCAs.

Trials conducted in third countries, including developing countries.

Session 3

Dossier maintenance, including substantial amendments.

Safety information, collection, reporting and review of safety information:

- expedited reports
- annual safety reports.

Databases:

- EudraCT
- EudraVigilance.

Inspections (GCP, GMP).

Session 4

Potential solutions and recommendations for the future, including views from patients, healthcare professionals and investigators:

- implementation within the current framework
- implementation requiring changes to guidelines
- solutions requiring changes to the legislation.

Session 5

Final views of stakeholders, with general discussion and conclusions.

Session 6

European Commission — Perspectives for the future.

3. KEY ISSUES ARISING FROM THE CONFERENCE PRESENTATIONS

The conference opened with a presentation of figures illustrating the current situation with regard to the numbers of patients involved in clinical trials in the EU, the US and other regions, and to financial investment in pharmaceutical research and development in the EU, Japan and the US.

Based on data from EudraCT, 80% of clinical trials conducted in the EU since 2004 have been by commercial sponsors and 20% by non-commercial sponsors.

Most of the trials are performed in multiple sites and multiple countries. A major question is how to ensure a favourable environment for clinical research in the EU, taking into account the complexity of the EU network.

The challenge in Europe is therefore to optimise our regulatory environment to:

- ensure protection of subjects participating in clinical trials (EU and third countries)
- ensure a framework for high-quality research in the EU and its acceptability worldwide (product development, product authorisation)
- promote a favourable research environment (clear, efficient and effective administrative and scientific procedures).

3.1. Scope of the legislation and definitions

Directives 2001/20/EC and 2005/28/EC have introduced a number of beneficial elements into the EU legislation, which were welcomed.

These establish a common legal framework for:

- interventional clinical trials of medicinal products in the EU
- compliance with good clinical practice (GCP) and good manufacturing practice (GMP)
- definitions of tasks, responsibilities and legal entities
- timelines and administrative processes
- improvements in the quality of research and the protection of patients.

However, the presentations and discussions revealed calls for a number of clarifications or changes to the legislation.

3.1.1. Scope of the legislation

The Directives have set out a legal basis for GCP compliance in the conduct of clinical trials. This has had the welcome result that in some Member States, there has been increased investment in the development of clinical-research infrastructure and the promotion of training programmes on clinical trials. As a result, increased awareness of the requirements for the conduct of clinical trials, including GCP, has led to improvements in the available infrastructure for clinical-trial management and improved GCP compliance.

The ethics committee speaker noted an increased implementation of GCP requirements in non-commercial clinical trials. The patients' representative reinforced this point, adding that the Directive promotes a more rational conduct of clinical trials and provides a greater level of patient protection in commercial and non-commercial trials.

Nonetheless, the lack of transparency and harmony in the application of GCP standards among Member States was raised as a concern. The GCP Inspectors Working Group recommended that there be a harmonised reference to ICH GCP as the EU standard in the EU legislation.

Sponsors' representatives considered that there should be an adaptation or interpretation of GCP standards (perhaps through specific annexes to the GCP guidance) according to the type of trial (purpose, characteristics), or in relation to the risk of the products for subjects (e.g. novel products, orphan products, marketed products or products used for minimal intervention). This approach would greatly facilitate the application of the requirements in these different situations. The particular needs of very large-scale clinical trials, involving many hundreds of sites and thousands of patients, were emphasised in this context.

Non-commercial sponsors noted that, whilst requirements for clinical trials of medicinal products are well regulated and relatively well harmonised, requirements for other biomedical research on human subjects are poorly regulated and lack harmonisation, leading to major discrepancies in the protection afforded to subjects and difficulties in setting up such trials. They called for the scope of the legislation to be widened to include all categories of biomedical research in human subjects (with or without health products, whether interventional or observational), and not only interventional clinical trials of medicinal products. It was recommended that both the GCP standards and harmonised administrative requirements should apply not only to clinical trials with investigational medicinal products but also to other types of trials, including those for in vitro diagnostics, medicinal devices, herbal medicinal products and homeopathic remedies, among others.

Further investment in the development of the clinical-research infrastructure and in the provision of training to all stakeholder communities in the EU will increase trial quality, improve GCP compliance of clinical trials and help to provide a strong stimulus for research in the EU.

3.1.2. Definitions

Commercial and non-commercial trials and sponsors

There was a clear consensus that there should be one set of GCP standards for all trials, and not different standards for commercial trials and for non-commercial trials. Non-commercial sponsors warned that the suggestion (in the draft guidance on specific modalities for non-commercial trials) that non-commercial trials might not always be acceptable in marketing-authorisation applications can be damaging to non-commercial research, and to investment in it. Trials conducted by non-commercial sponsors should be admissible for marketing authorisation application purposes. There are many examples of where such trials have been very important to the development of medicinal products and their marketing authorisation, and to the development of the use of medicines in practice.

Rather than a distinction between commercial and non-commercial trials, the idea of a differential application of the legislation, using a risk-based approach, was proposed. This approach should be based on the risk involved in the trial and on the extent of knowledge of the product (e.g. novel product, marketed product, marketed product used within its

summary of product characteristics (SmPC), etc.), thus avoiding the development of double standards in terms of GCP compliance and the quality and credibility of data (refer also to the paragraphs on GCP in section 3.1.1.). This approach would prevent the perception of there being two levels of quality in the present legislation and in its implementation, as seen in the current 'Draft guidance on specific modalities for non-commercial trials'. It would lead to a general improvement in the quality and cost-effectiveness of trials (e.g. better prioritisation of monitoring and of other quality-control activities).

The non-commercial sponsors expressed serious concerns about the cost to them of implementing various aspects of the legislation and its administrative procedures. They consider that this cost has reduced the number of independent trials. Non-commercial sponsors should benefit from waiving of fees for applications to ethics committees and NCAs, waiving of the obligation of the sponsor to supply the IMP free of charge when it has a marketing authorisation, support in SUSAR reporting, harmonisation of insurance requirements, and insurance coverage by the public health systems. An EU regulatory affairs helpdesk, aimed at supporting non-commercial sponsors, was also proposed.

Proposals to improve the cost-effectiveness of non-commercial trials without reducing GCP compliance included adapting record-keeping and monitoring requirements (e.g. by web-based trial master files/investigator site files, and by developing models of monitoring and audit adapted to the structures or their organisations and the risk of the trials).

Non-commercial sponsors explained that the European Science Foundation – European Medical Research Councils (ESF-EMRC) is initiating a 'Forward Look' activity entitled 'Investigator Driven Clinical Trials' during 2007/2008 to develop key recommendations on better coordination of the various national and European initiatives in this domain and on strengthening investigator-driven clinical trials in Europe in an international perspective.

Other issues raised included the potential role of non-commercial sponsors in providing independent research on topics such as safety and combination therapies, and suggestions that one of the pivotal pre-authorisation studies should be performed by an independent non-commercial sponsor.

Interventional and non-interventional trials

Sponsors' representatives pointed out that there are divergent interpretations at Member State level of the definition of interventional and non-interventional studies, and that, as a consequence, the same post-marketing study may be regarded as an interventional clinical trial in one Member State and as a non-interventional study in another. These differences mainly relate to the interpretation of what constitutes 'intervention' in terms of blood samples, questionnaires or other measurements. A proposal was made for the creation of an intermediate category of trials between interventional and non-interventional — perhaps to be called 'minimally interventional' — with only low-risk intervention and without clinical-trial authorisation by national competent authorities, but with a favourable opinion of the ethics committee required.

The lack of a precise non-IMP definition (see 'Investigational medicinal product', below) leads to disharmony between NCAs with respect to the classification of trials as (non-)interventional, since the diagnostic and/or monitoring procedures are not classified in the same way across the Member States.

The NCAs share the sponsors' concern over the difficulty in interpreting this aspect of the legislation.

Substantial and non-substantial amendments

There was a consensus among stakeholders (sponsors, NCAs and ethics committees) on the need for further guidance to ensure consistency across Member States in the classification of substantial and non-substantial amendments. In addition, guidance is needed on whether NCA and/or ethics committee approval is required. Speakers for the CTFG highlighted the current work of this group on the preparation of a proposal for further guidance or Q&A text, to include different examples.

Investigational medicinal product (IMP)

All stakeholders expressed concern about the difficulties in interpreting the definition of IMP. It is not clear to what extent these can be remedied in the context of the existing definition and to what extent the definition itself may need some revision. It was pointed out that there is divergence among Member States, with the result that, in a multistate trial, a treatment might be considered to be an IMP by some NCAs and not by others. In addition, it was considered that the concepts applying to other medicinal products used in clinical trials and referred to as 'non-investigational medicinal products' (NIMPs) have no clear legal basis. Particular difficulties arise in relation to: the obligation of the sponsor to provide the IMP free of charge; the labelling requirements; and the SUSAR reporting requirements, all of which can add a large financial and organisational burden if a product is classified as an IMP. The CTFG pointed to the availability of the 'Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials', published recently by the Commission in EudraLex Volume 10. It was not clear whether this would be an adequate solution to the problems encountered, partly because the guidance had only been published recently.

Off-label use of products is often the standard of care in routine clinical practice in many paediatric and oncological settings. It is a cause of particular concern to sponsors (to non-commercial paediatric and oncology research groups and to commercial sponsors) that these products may be classified by some NCAs as IMPs when they are neither the test nor comparator per se. They would be considered background treatments based solely on the trial design but become IMPs due to the off-label nature of their use.

There are differences in interpretation of marketing-authorisation status (pre- versus post-authorisation), with some NCAs recognising a marketing authorisation anywhere in the EU whereas others consider only the national marketing-authorisation status in their territory.

Sponsor

Confusion around the concept of 'single sponsor' for a trial was an issue of major concern throughout the EU, raised mainly by non-commercial sponsors. The problems they encounter represent a major obstacle to the initiation of multinational, collaborative clinical research by academic institutions. Academic institutions typically lack the legal and infrastructural capacity to fulfil, within a single organisation, the sponsor's tasks in multinational trials. Sponsors said there is a need, therefore, to allow multiple sponsorship of both multinational and national trials, whereby the roles, responsibilities and liabilities in the various Member States are shared on a contractual basis between the organisations/institutions/persons involved (including third-country non-commercial sponsors).

Legal representative of the sponsor

Contract research organisations (CROs), in particular, raised concerns about the concept of 'legal representative' and its implications. They reported that it is very difficult to get

clear advice on the real role and liability of a legal representative. It was proposed to replace the concept with that of an 'authorised representative' or 'agent of the sponsor' instead, with civil and criminal liability being retained by the sponsor. In addition, clear guidance on the roles and responsibilities of the sponsor and this authorised representative should be provided.

Non-commercial sponsors also have trouble with the concept of legal representative, where third-country non-commercial sponsors have difficulties establishing a legal representation in the EU.

Research contracts with investigators/institutions

CROs also stated that it would greatly improve the efficiency of research and the setting-up of trials in the EU if investigator/institution contracts could be based on a standard template established in each Member State.

3.1.3. Summary of recommendations in relation to the scope of the legislation and its definitions

Proposed measures within the current legal framework:

- Provide harmonised and clear guidance, and ensure pan-EU agreement on the interpretation of IMP/non-IMP.
- Provide harmonised guidance and ensure pan-EU agreement for consistency across Member States regarding substantial and non-substantial amendments, the process for notification of substantial and non-substantial amendments to the NCA and the ethics committee, and clarification on whether NCA and/or ethics committee approval is required.
- Improve communication on harmonised GCP standards, with mechanisms in place for input from stakeholders on issues of divergence among Member States.
- Apply GCP standards in an adapted manner to different categories of product, based on the risk and extent of knowledge available (e.g. novel products, products with a marketing authorisation, products with a marketing authorisation used according to the SmPC) and avoiding the introduction of double standards for the quality of commercial and non-commercial research.
- Guidance on the role and responsibilities (and liabilities) of the legal representative, and on how the entity should be established.
- Development of standard templates for contracts between the sponsor/CRO and the investigator/institution at Member State level.
- Explore the possibility of multiple sponsorship of a single clinical trial within the present legal framework.
- Ensure that research by non-commercial sponsors is admissible for marketing-authorisation purposes.
- There should be no double standards for the quality of commercial and non-commercial research. However, non-commercial sponsors should be given support, due to their limited financial and infrastructural resources, through:
  - waiver of fees for applications to ethics committees and NCAs

- waiver of the obligation to supply the IMP free of charge when it has a marketing authorisation
- support for SUSAR reporting
- harmonisation of insurance requirements and insurance coverage by the public health system
- establishment of an EU regulatory affairs helpdesk for clinical trials
- cost-effective models for trial master files/investigator site files, monitoring and auditing, with reduction of GCP compliance or data quality.

- Investment in the development of clinical-research infrastructures and in the training of all stakeholder communities, in particular for the benefit of non-commercial organisations and for investigators and their support staff.

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

- A single legislative framework for all biomedical research on human beings, with or without health products, interventional or observational; preferably in the form of a regulation rather than a directive.
- Adapt the legislation in different ways according to the risk involved in the trial and the extent of knowledge of the product:
  - define categories of research and products, based on risk involved
  - develop a regulatory requirement based on the risk associated with each category
  - organise workshops to reach agreement on categories.
- Revise the definition of interventional and non-interventional trials to introduce the concept of 'minimally interventional trials', in order to facilitate post-authorisation studies.
- Remove the concept of commercial and non-commercial trials, to remove any perception of, or actual, dual standards of GCP compliance and data quality.
- Include a clearer framework for the CPMP/ICH/135/95 GCP guideline in the Directives and their implementing texts.
- Establish a basis for multiple sponsorship of a single trial, with sharing of responsibilities. (Also consider the possibility of this within the present legal framework.)
- Establish a concept of authorised representative instead of legal representative, with civil and criminal liability retained by the sponsor.
- Revise the definition of IMP and reduce the scope of products that fall within this definition in a clinical-trial setting.
- Clarify the non-IMP concept, especially when authorised medicinal products are used as standard therapy in ways different to those foreseen in the SmPC.

3.2. Clinical-trial application and review process

Improvement of the application process for clinical trials was considered to be one of the benefits of Directive 2001/20/EC. The application process was considered more predictable, clearer, and more consistent and standardised, resulting in reduced timelines for the review of applications and substantial amendments by NCAs and ethics committees in most Member States. The NCA and ethics committee review processes run in parallel in most countries.

Advantages cited included:

- the unique identifier for a clinical trial in the EU (the EudraCT number)
- the common (EudraCT) clinical-trial application form accepted in most Member States
- the common IMP dossier (IMPD) accepted in most Member States
- guidance documents with details on the content of the CTA and IMPD
- clear timelines in most Member States.

European CROs have had positive experiences with the acceptance of a common IMP dossier by most NCAs. Thorough completion of the IMPD results in the generation of robust and reliable data.

The legislation has also improved the ethics committee review process, and interaction between the NCAs and ethics committees has become more harmonised. The CTFG representatives also highlighted the importance for the clinical-trial application (CTA) review process of sharing information through EudraCT and its alert system, so that NCAs are aware of the decisions and activities of other NCAs. This promotes harmonisation of the scientific assessment process, and the sharing of experience and interpretations, thus promoting harmonisation and improving the safety of research participants. The different cultural and ethical requirements across and within Member States remain an issue that is difficult to solve through legislation.

Despite the gains achieved through the implementation of the legislation, there were many concerns that the promises of the Directive had not been fulfilled, particularly with respect to the insufficient harmonisation of administrative processes. There remain differences between Member States in the IMPD requirements (some countries have specific national requirements, some do not accept the common CTA form) and a lack of transparency about the Member State requirements. There are also differences in timelines between Member States, including validation periods and clock-stops added to the 60 days provided for in the Directive. Sponsor representatives consider that greater efficiencies need to be achieved. In particular, there is a need to reduce the administrative burden associated with applying for the same clinical trial across multiple Member States, which results from having to be aware of, and comply with, multiple differences in the detail of the processes.

It is important to note that where differences in requirements or timelines arise, even between a minority of Member States, this still causes a significant increase in the burden on applicants/sponsors.

It was noted that although the CTA form is harmonised for most NCAs, there has not been the same progress for ethics committee submissions, where there are additional differences in documentation requirements.

Commercial and non-commercial sponsors highlighted a number of specific issues, with the latter finding it especially difficult to maintain an oversight of the particularities of each Member State's requirements. This difficulty is also encountered by small and medium-sized enterprises (SMEs), and by those third-country sponsors who do not have a major presence in the EU. Commercial sponsors, on the other hand, generally have dedicated regulatory affairs departments with the necessary resources to track the national differences.

3.2.1. Availability and transparency of information

In the short term, and awaiting further harmonisation, detailed information on all national requirements should be available in English and at a single point (website). The CTFG representatives clarified that its CTA subgroup is collecting national CTA requirements for the purposes of harmonisation.

Sponsors requested a one-stop shop (pan-EU office/helpdesk) to provide advice and support to applicants, and to monitor and provide rapid resolution of issues where difficulties in implementation and/or disharmonies are identified.

3.2.2. Clinical-trial application

The burden of paperwork should be reduced by rationalising the application forms and the content of dossiers and by reducing the number of times the same or nearly the same information has to be submitted to different NCAs and ethics committees. The EudraCT form should be improved to make it more user-friendly.

A clear definition of an IMP (see also 3.1.2 above) would assist in clarifying the data required to support applications for different types of IMP and non-IMP.

The overall aim should be for Member States to comply with a single common CTA form with harmonised data requirements for all NCAs and ethics committees, and to have a single electronic submission point through the EudraCT portal. This single submission point should be for both the CTA form and the supporting IMPD and study documentation.

3.2.3. Review procedure

Recommendations were made that the review process be streamlined further, in particular for multistate clinical trials. Recommendations covered the following range, all based on a need for a single harmonised dossier and review procedure:

- shared assessment by the concerned Member States with an agreed outcome
- mutual recognition or decentralised procedure
- centralised procedure.

Such an approach would avoid duplication of assessments, saving time and human resources, would reduce the administrative burden and the perception of difficulty in conducting clinical trials in the EU, and would ensure that a common CTA and IMPD were maintained throughout. Moreover, it would provide greater predictability of the review outcome for marketing-authorisation applications at a later stage.

NCA representatives did not support the concept of a centralised procedure for authorisation of clinical trials, since the national particularities should be taken into account as well.

The CROs indicated that ideally there should be an EU regulation that establishes a unified, comprehensive and fully integrated standard for clinical trials with medicinal products for human use, with a process where approval of an application for a multi-national trial by a single competent authority and a single ethics committee (plus the involvement of local ethics committees to assess the suitability of the site for the study) would permit initiation of the trial across the whole of the EEA. Non-commercial sponsors also considered that a regulation would be preferable.

Regarding the single ethics committee opinion, different views were expressed during the conference from the different stakeholders, but it was generally recognised that a single national-ethics-committee opinion is preferred. This should nonetheless be based on a common dossier and application form.

3.2.4. Assessment process

There were calls for more-harmonised and coordinated assessments by ethics committees and NCAs. Pan-EU training for NCA assessors and ethics committee members was recommended, to facilitate scientific consistency and information requirements and to improve patient protection.

There should be a clear identification of the roles and responsibilities of ethics committees and NCAs in order to avoid duplication of work between the two bodies (i.e. NCA assessing the medical and scientific merit of the trial, whereas the ethics committee would determine whether the protocol meets the ethical standards, is in line with the medical practice of a given country, preserves the rights and integrity of trial subjects, and assess the suitability of the site concerned). This clarification of the roles and responsibilities of the ethics committees and NCAs should include more guidance on the interactions between them.

One major issue is the lack of harmony in the assessment of substantial/non-substantial amendments as well as in the definition of these (see 3.1.2 above) by both NCAs and ethics committees.

The CTFG recognised the need for further communication on, and harmonisation of, scientific assessments and related processes, and considered this achievable within the current CTFG framework.

3.2.5. CTFG

There was a call for strengthening of the role of the CTFG by giving it legal status and a clear mandate to coordinate the CTA application and review process, including the possibility of arbitration between Member States, and for the establishment of processes for sponsors to appeal decisions.

Greater transparency regarding the objectives and workplan of the CTFG and a systematic involvement of the stakeholders were also called for.

3.2.6. Timelines

The sponsor and CRO groups asked for compliance with the legal timelines for review set out in the Directive, without additional pre-submission and clock-stop mechanisms.

Concerning amendments, the CROs recommended the introduction at EU level of:

- a maximum time for review of substantial amendments by the NCAs (as has been done in the legislation of some Member States), in order to avoid delays in approvals
- an expedited process for review and implementation of 'efficacy' amendments by NCAs and ethics committees (e.g. to permit rapid closure of a trial arm that is not proving effective).

3.2.7. Summary of recommendations concerning the clinical-trial application and review process

Proposed measures within the current legal framework:

- Ensure national requirements are readily available in English, and through a single source (website).
- One-stop shop (pan-EU office/helpdesk) to provide advice and support to applicants (to ethics committees and NCAs), and to monitor and provide rapid resolution of issues where difficulties in implementation and/or disharmonies are identified.
- Single and unique CTA form and dossier (also for substantial amendments), with harmonised data requirements for all NCAs and ethics committees.
- Guidance that defines the relative roles and responsibilities of ethics committees and NCAs.
- Guidance on interaction between ethics committees and NCAs.
- Harmonised assessment methodologies for ethics committees and NCAs.
- Provide pan-EU training for assessors and ethics committee members, to facilitate consistency in approach.
- Strengthen the role of the CTFG for the harmonisation of the CT application and assessment process.

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

- Single point of entry for submission of CTA applications (form and dossier), e.g. single submission point through EudraCT portal.
- Enforce legal timelines for review and add a maximum timeline for the review of substantial amendments by the NCAs.
- Streamlined review processes: shared assessment, mutual-recognition/decentralised procedure or centralised approval system with provision for a single assessment by one competent authority, valid for multistate trials.
- Specialisation of NCAs in particular types of health product in the context of a streamlined application and authorisation procedure.
- Provide legal status for the CTFG.

3.3. IMP and GMP issues

The establishment of common GMP requirements for IMPs, the role of the QP (qualified person) responsible for batch release and the acceptance of the IMPD were all welcomed. The problems raised result mainly from differences between Member States in the interpretation of these requirements, and from the absence of guidance in some specific areas. Transparency in the area of country-specific conditions for an IMP dossier would also be welcomed, although fulfilment of these requirements can be complicated for some sponsors and CROs, and harmonisation is much preferred.

The experience of the non-commercial and the commercial sponsor representatives as well as the speakers for NCAs to date shows that amendment of the IMP definition (see 3.1.2) and harmonisation of GMP requirements are key areas that need to be addressed urgently.

3.3.1. GMP

It emerged that the various additional requirements of the individual NCAs for the scope of the IMP manufacturing licence and labelling requests have been introduced, and these must be followed by the pharmaceutical industry regardless of the requirements of the Clinical Trials Directive.

The commercial sponsors proposed involvement of the GMDP Inspectors Working Group in addressing a number of issues, including:

- varying levels of acceptance by NCAs of the QP declaration of GMP compliance of a third-country manufacturer
- definition of the content of the QP declaration (the absence of a definition has led to the generation of apparently non-compliant documents)
- classification of what is a manufacturing process, e.g. the reconstitution of an IMP in water immediately before its use, or administration of a precursor of a radionuclide with an extremely short half-life
- distinction between the responsibilities of the QP and the sponsor's legal representative in case of quality defects.

The CROs and commercial sponsors also called for harmonisation of requirements for the importation of an IMP, and for elimination of the separate submission of the importation certificate after trial approval. They struggle to comply with the country-specific requirements for IMP labelling, stability testing and testing of comparators originating from third countries.

The NCAs welcomed the concept of a common IMP dossier submission and expressed a positive experience overall. They are concerned about differences in the areas of QP activities and documentation required, IMP labelling, and GMP-compliance documentation. The NCAs consider that a dedicated meeting of the CTFG, GMDP IWG and European Commission would be beneficial in resolving a number of the current problems.

3.3.2. Summary of recommendations in relation to IMPs and GMP

Proposed measures within the current legal framework:

- Modify labelling requirements for IMPs to allow any commercially available medicinal product marketed for adult use to be used as IMP in paediatric clinical trials in multiple Member States.
- Clarification and guidance regarding the roles and responsibilities of QP and legal representative (e.g. in the context of quality defects).
- Elimination of the separate submission for import licence by including importation authorisation within the NCA's approval of the clinical trial application.
- Simplify and harmonise requirements for the testing of comparators originating from third countries (may also require some modification of the legislation).
- Improve acceptance of the QP declaration of GMP compliance of a third-country manufacturer.
- Define the content of QP declarations and batch-release certificates.
- Eliminate national differences in IMP-labelling requirements.
- Clarify and harmonise stability-testing requirements.
- Improve classification of what activities (e.g. reconstitution) fall under GMP and require GMP authorisation, and what activities do not.
- Involve the CTFG, GMDP IWG and European Commission in discussions/workshop to find solutions to labelling, QP role and documentation, and GMP-related issues.
- Develop mechanisms to ensure that the assessment of trial methodology by ethics committees and NCAs is of high quality and can contribute to reducing the risk of trial design errors (both random and systematic errors).

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

- Revise labelling requirements.
- Revise the definition of IMP (see 3.1.2).
- Develop uniform GMP requirements for all IMPs, including advanced therapies, gene and cell therapies, and radiotherapy products (suggested by non-commercial sponsors and CROs).

3.4. Ethics committees

The Directives have established clear requirements for the role of ethics committees in the protection of participants in clinical trials. They have set up the requirement for a single opinion on ethics per Member State for multi-centre trials. In order to achieve this single opinion many Member States have put in place appropriate procedures and established provisions for the functioning of the ethics committees based on common guidelines. The creation of a single ethics committee in the few Member States where legal regulation did not previously exist was also received very positively. During the conference, these

requirements were welcomed, and this approach was considered adequate in the context of national differences of culture and ethics.

Although some sponsors asked for further centralisation of ethical review at EU level, there was much support for the system of a single opinion per Member State. It was considered that the legal framework should reflect the need to respect national, cultural and therefore ethical differences across the EU, though ethical principles should be universal. There should be standard requirements for administrative processes, forms and dossiers. There might be a role for a European body to develop consensus guidance on specific ethical issues, such as use of placebo or clinical trials in the context of emergency care.

The large majority of attendees, in particular patients' representatives, considered that the implementation of the Directives has resulted, overall, in better protection of human subjects in clinical trials. A key benefit of the legislation is the single ethics opinion per Member State, which is a real improvement and has generally resulted in shorter times for provision of ethics-committee opinions within the EU.

Ethics committee representatives stressed there is "no ethic without methodology or methodology without ethic". Ethical review should be independent.

During the discussion, ethics committee representatives stressed the importance of maintaining the current public trust in ethics committees.

Concerns remain in a number of areas, including:

- lack of infrastructural support available for ethics committees
- burden of safety-reporting requirements on all parties, with limited benefit
- need to address specific situations such as consent in emergency-care settings
- differences between Member States in application forms and dossier requirements for submission to ethics committees
- complex interactions between local and regional/national committees in arriving at a single opinion
- access to information for ethics committees, in particular the EudraCT and EudraVigilance databases
- need for clarity on the applicability of GCP requirements to ethics committees.

There was a widespread view among speakers and attendees that national implementation of the legislation and guidance on ethics committees has been heterogeneous.

Non-commercial sponsors proposed an EU coordination role for the development of common standards, tools and procedures for ethics committees. It was suggested that a conference to develop this topic should be organised.

3.4.1. Applications to ethics committees

Sponsors requested further standardisation of ethics committees' requirements for data and application formats (paper or electronic). The diversity of these requirements and the complexity of national processes add to the burden on researchers (and on the ethics committee structures), especially where local ethics committees are involved in reaching the single opinion. In this context, ethics committee representatives also commented on the need for a correct balance between central opinion and local knowledge.

Sponsors would also like those requirements to be more transparent — for example through the existence of a one-stop shop — and would like it to be possible to submit the same dossier to a single point in the Community for both ethics committees and NCAs (EudraCT portal) (see 3.1.2).

Another problem, raised by sponsors, concerns the operation in some Member States of a process of sequential review by the NCA and ethic committee — a process that extends timelines.

The individual responsibilities and interactions between the NCA and ethics committee should be clarified (e.g. for the assessment of SUSARs).

3.4.2. Structure and procedures

In most Member States, multiple ethics-committee structures exist. Their interaction often induces complex procedures, extends the timelines required for the adoption of the single opinion, and creates the potential for duplication of work.

The Directive and its implementation have not changed the status quo as far as the constitution of the membership of ethics committees is concerned. There are no specifications in the Directive on this point, despite it being addressed in the GCP guideline. There are some legal and institutional requirements at national or committee level, but it is not always easy for ethics committees to find the appropriate balance of members or experts, e.g. a mix of medical and lay members, lawyers or philosophers familiar with the fields of clinical trials and of ethics.

Patients' representatives also expressed the wish to have more systematic participation in ethics-committee activities. They pointed out that patients may have a different perception, compared to medical experts or other parties, of the risks and discomforts they are prepared to tolerate in particular situations.

There is a need to provide ethics-committee members and experts with more training on the law, the methodology and the ethics of clinical trials.

The GCP Inspectors Working Group noted the need to include in the Directive a set of provisions (or a reference to those provisions) that ensure that the requirements set out in the GCP guidelines are applicable to ethics committees in the context of the EU legislation.

3.4.3. Guidance on issues of common ethical concern

Commentators indicated that it would be very helpful for individual ethics committees, and for consistency of ethical review, to have universal guidelines on ethics defined at EU level (e.g. in relation to: use of placebo; clinical-trial designs, such as those where dose interruptions are foreseen; and informed consent, especially of vulnerable subjects).

3.4.4. Access to information

Ethics committees asked for direct access to EudraCT and EudraVigilance in order to optimise their oversight of clinical trials. This would help ethics committees to ascertain promptly the status of, and updated information on, a clinical trial. They also requested better information on, or involvement in, inspections (see sections 3.7.1 and 3.7.2).

3.4.5. Infrastructure

In many cases, ethics committees have very limited resources. Members are generally voluntary and perform their committee duties in addition to their principal activities. The financing of ethics committees is an issue that has been addressed differently in different Member States. In some cases, this has involved the establishment of a fee for application to the ethics committee. When it is requested, there is usually the possibility of a waiver for non-commercial sponsors.

Ethics committees consider that their available resources are often absorbed in the management of paperwork resulting from large numbers of dossiers, substantial amendments, safety reports, etc., and in the maintenance and archiving of records of applications, meeting minutes and deliberations of the committees, and of their procedures. There is a need to reduce unnecessary submission of information or duplication of activities (e.g. between ethics committee and NCA), and steps should be taken to ensure that ethics committees have adequate support staff, members and resources (e.g. space for files and records).

3.4.6. Safety reporting to ethics committees, including SUSAR reporting

The large number of individual suspected unexpected serious adverse reaction reports (SUSARs) received by ethics committees places an enormous burden on them. This excessive and unnecessary amount of information cannot be effectively reviewed. Furthermore, it does not provide concise safety data that would better protect trial subjects.

The SUSARs are usually provided without any additional information or analysis to put them in the overall context of the clinical trial(s), IMP-safety profile and patient population. The same reports are submitted to NCAs and to other ethics committees. The considerable effort involved in processing the paperwork is not matched by adequate structures for review of the information, and the resource could be put to better use.

Annual safety reports are lengthy documents and are provided to multiple ethics committees. Within one Member State, more than one ethics committee may have reviewed the clinical trials addressed in a single annual safety report. Again, better processes are needed to ensure that these are adequately reviewed by, or on behalf of, the ethics committees, and by people with the necessary expertise, role and resources.

The topic of safety reporting, including to ethics committees, is addressed in more detail in section 3.5.

3.4.7. Informed consent of subjects

Patient representatives asked for further harmonisation on the presentation of ‘informed consent’ across the EU, in terms of both the quality and quantity of the information provided.

Delegates noted concern about trends in some cases to provide exhaustive and excessive amounts of information to patients, such as long lists of potential adverse reactions, which contribute little towards truly informing the patient and which are intended rather to address liability concerns of the sponsors.

They also noted that the legislation does not regulate what happens at the end of a trial, in terms of continuation of the treatment or publication of the trial.

The requirements for informed consent as currently set out hamper research in situations of medical emergency. Some Member States have consequently instituted national rules, which can be particularly problematic for performing multi-centre trials in several Member States. In other Member States, trials in situations of medical emergency may be difficult or impossible to conduct.

Another concern expressed by patients' organisations is the difficulty they have experienced in designing studies that comply strictly with ethical requirements in the field of rare diseases, where the usual requirements for confidentiality may not be practicable.

3.4.8. Summary of recommendations in relation to ethics committees

Proposed measures within the current legal framework:

- Member States should establish a single, national ethics-committee review and opinion, by clarifying, where necessary, the responsibilities of central and local ethics committees, and by rationalising the procedures to be followed by committees and applicants.
- The composition of ethics committees should be further defined, consistent with ICH GCP requirements, and appropriate involvement of medical and other experts and laypersons, including patients, should be established.
- Further education and training for ethics-committee members and their support staff should be established to reinforce capacity for scientific and ethical review.
- Quality assurance systems should be put in place to ensure consistency of ethics committees with requirements such as GCP principles. This might include systems for accreditation of ethics committees, self-evaluation, etc.
- Establish an EU coordination role for the development of common standards, tools and procedures for ethics committees.
- Organise a conference to further support the development of these common items.
- The GCP IWG proposed that ethics committees should be subject to GCP inspection.
- Establish a common application form and dossier for all ethics committees.
- Provide common EU guidance on the process for waivers to informed consent in emergency settings.
- Establish guidelines on ethics at EU level (e.g. in relation to: use of placebo; clinical-trial designs, such as those where dose interruptions are foreseen; informed consent, especially of vulnerable subjects; etc.).
- The separate roles and responsibilities of ethics committees and NCAs should be clarified, following the principle that the NCAs should focus on the product and ethics committees on the person.
- Necessary resources for the ethics committees — in terms of finance, training and administrative support — should be ensured at national level and, where applicable, at EU level (e.g. aspects of training, coordination and communication/information sharing, development of common standards, IT infrastructure, etc.).

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

- To enforce or make mandatory some or all of the above-mentioned recommendations, e.g. composition of ethics committee, where appropriate.
- Amend the legislation to ensure a workable process for consent in clinical trials in emergency settings, including, where necessary, waiver of consent.
- To give ethics committees direct access to EudraCT and EudraVigilance databases.
- To reinforce the role of ethics committees, e.g. by entitling them to suspend a clinical trial temporarily, for example whilst awaiting clarification on a safety or inspection issue.
- Establish provisions to ensure the applicability of ICH GCP requirements to ethics committees.
- Reinforce the obligations to ensure the necessary infrastructure and resources are available to ethics committees.

3.5. Safety reporting in clinical trials

The topic of safety reporting in clinical trials was one of the most intensely discussed of the day, by all stakeholders. This issue was referred to in almost all presentations and was extensively debated during the discussions.

Directive 2001/20/EC has brought a welcome and potentially coherent set of definitions and requirements, and has opened the way to electronic reporting of SUSARs. Beneficial elements include:

- definitions of adverse reactions and of SUSARs
- annual safety reports
- use of EudraVigilance
- use of international birth date for annual safety reports once the product has received a marketing authorisation somewhere in the world
- common EU guidelines on adverse reaction reporting (expedited and annual).

The provisions for reporting timelines, electronic reporting and the EudraVigilance database were regarded as positive contributions of the Directive, although the lack of harmonised implementation of these rules across the Member States remains a major problem. Although the Directive defines the responsibilities regarding transmission of safety information to the NCAs, ethics committees and investigators, there are still too many different interpretations made by Member States of some safety definitions and reporting requirements.

Non-commercial sponsors stated that the current system of safety-information collection, reporting and review is unnecessarily complex, especially for multinational trials, and this results in a great administrative and bureaucratic burden for both the sender and the receiver, without a commensurate contribution to improving study-subject safety.

Commercial sponsors considered the safety guidelines on reporting to investigators involved in the clinical trials ineffective, as these are applied differently by Member States and vary at national level from the expedited submission of all safety reports to generation of country-specific periodic listings of selected cases. The situation is similar across the

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.

Georgette Lalis

Director, Directorate for Consumer Goods,

Directorate-General for Enterprise and Industry,

European Commission.

ANNEXES

Annex A Conference programme

Annex B List of registered attendees

Annex C Further conference-related documents

Annex A Conference programme

Presenters and topics

SESSION	PRESENTER	TOPIC
Session 1	Thomas Lönngren, EMEA	Opening statement, objectives, and background
Session 2	**Session chair:** Rui Santos Ivo - European Commission DG Enterprise **Session co-chairs:** Stefan Bielak – ESF/Olgahospital Stuttgart, Germany Birgitta Pettersson – MPA, Sweden **Speakers:** Commercial sponsors Alan Morrison - EuropaBio/Amgen, UK Non-commercial sponsors Monique Podoor – EORTC, Belgium NCA Hartmut Krafft – PEI, Germany Ethics committees Michael Fuchs – EUREC/University of Bonn Trials in developing countries Fernand Sauer – Honorary Director General of the European Commission	Scope of legislation Definitions Clinical-trial authorisation and IMP dossier: ▪ To ethics committee ▪ To competent authority IMP-related issues (definitions, labelling, GMP, etc.) Ethics committee structures and processes Competent authority processes Roles of ECs and NCAs Trials conducted in third countries, including developing countries
Session 3	**Session co-chairs:** Helena Beaumont – INFARMED, Portugal Detlef Niese –EuropaBio/Novartis Pharma, Switzerland **Speakers:** Commercial sponsors Gaby Danan – EFPIA/Sanofi-Aventis, France Non-commercial sponsors Stefan Bielak – ESF/ Olgahospital Stuttgart, Germany NCA Brian Davis – MHRA, UK Pierre Henri Bertoye – AFSSAPS, France Ethics committees Dominique Sprumont –EUREC/University of Neuchâtel	Dossier maintenance, including substantial amendments Safety information, collection, reporting and review of safety information: ▪ Expedited reports ▪ Annual safety reports Databases: ▪ EudraCT ▪ EudraVigilance Inspection (GCP, GMP)

Session 4	**Session co-chairs**: Christine-Lise Julou – EFPIA, Belgium Tamás Paál – OGYI, Hungary **Panel members**: Including the morning session chairs and co-chairs: Large-scale clinical trials Rory Collins – CTSU Oxford, UK Investigators Silvio Garattini, 'Mario Negri' Institute for Pharmacological Research, Italy Jacques Demotes, ECRIN/ESF, France Commercial sponsors John Poland – ACRO/Covance, UK Dagmar Chase – EUCROF/Clinrex, Germany Patients Nikos Dedes - Patients and Consumers Working Party Non-commercial sponsors Patrick Schöffski – EORTC, Belgium Commercial sponsors Alan Morrison – EuropaBio/Amgen, UK Mats Ericson – EFPIA /Wyeth Research, France Ethics committees Ritva Halila – EUREC/NCA Finland NCA Chantal Belorgey – AFSSAPS, France	Potential solutions and recommendations for the future, including views from patients, health professionals and investigators: ▪ Implementation within the current framework ▪ Implementation requiring changes to guidelines ▪ Solutions requiring changes to the legislation
Session 5	**Session chair:** Georgette Lalis – European Commission, DG Enterprise **Session co-chair:** Kent Woods – MHRA, UK Panel members: One senior speaker each from: Commercial sponsors Andrea Rappagliosi –EuropaBio/Merck Serono International, Switzerland Susan Forda – EFPIA/Lilly Industries, UK Patients Nikos Dedes – Patients and Consumers Working Party	Final stakeholders' views with general discussion and conclusions

	Non-commercial sponsors Jacques Demotes – ECRIN/ESF/EMRC, France Ethics committees Francois Chapuis – EUREC/Hospices Civils de Lyon Octavi Quintana-Trías – European Commission, DG Research NCA Kent Woods – MHRA UK	
Session 6	Georgette Lalis – European Commission, DG Enterprise	Perspectives for the future

Annex B List of registered attendees

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Dr	Pettersson	Birgitta	Clinical Trials Facilitation Group (CTFG)	Medicinal Products Agency	Sweden
Mr	Santos Ivo	Rui	European Commission, DG Research	European Commission, DG Enterprise	
Prof	Woods	Kent	National competent authority	Medicines and Healthcare Products Regulatory Agency (MHRA)	UK

Speakers and panellists

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Dr	Danan	Gaby	European Federation of Pharmaceutical Industry Association (EFPIA)	Sanofi-Aventis	France
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Title	Surname	Name	Organisation		Country
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Title	Surname	Name	Organisation		Country
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Title	Surname	Name	Organisation		Country
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Title	Surname	Name	Organisation		Country
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Title	Surname	Name	Organisation		Country
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Title	Surname	Name	Organisation		Country
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Title	Surname	Name	Organisation		Country
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Annex C Further conference-related documents

More documents relating to the conference are available through the 'Conferences & Events' section of the EMEA website:

http://www.emea.europa.eu/meetings/conference.htm

These include:

- Presentations made during the conference
- Written submissions received from interested parties
- Biographies
- Questions & comments received after the conference