# Appendix C-1

# Presentations

The presentations given during the meeting are provided in the sequence in which they were given.

Please note that some panellists did not have slides, so for them no presentation is available.

**Presentations in order of the conference programme**

Mr Thomas Lönngren – European Medicines Agency

Mr Alan Morrison – EuropaBio/Amgen, United Kingdom

Dr Monique Podoor – EORTC, Belgium

Dr Hartmut Krafft – Paul-Ehrlich Institute, Germany

Dr Michael Fuchs – EUREC/University of Bonn, Germany

Mr Fernand Sauer – Honorary Director General of the European Commission

Dr Gaby Danan – EFPIA/Sanofi-Aventis, France

Prof Dr Stefan Bielack – ESF/Olgahospital Stuttgart, Germany

Dr Brian Davis – CTFG/MHRA, UK

Mr Pierre Henri Bertoye – AFSSAPS, France

Prof Dr Dominique Sprumont – EUREC/University of Neuchâtel, France

Prof Rory Collins – Clinical Trial Service Unit,University of Oxford, United Kingdom

Prof Silvio Garattini – `Mario Negri` Institute for Pharmacological Research, Italy

Prof Jacques Demotes – ECRIN/ESF/INSERM, France

Dr John Poland – ACRO/Covance, UK

Mrs Dagmar Chase – EUCROF/Clinrex GmbH, Germany

Mr Nikos Dedes – Patients and Consumers Working Party,
European AIDS Treatment Group, Belgium

Mr Alan Morrison – EuropaBio/Amgen, United Kingdom

Dr Mats Ericson – EFPIA/Wyeth Research, France

Ms Ritva Halila – EUREC/Ministry of Social Affairs and Health, Finland

Dr Chantal Belorgey – CTFG/AFSSAPS, France

Prof Dr Stefan Bielack – ESF-EMRC/Olgahospital Stuttgart, Germany

Prof Jacques Demotes – ECRIN/INSERM, France

Dr Francois Chapuis – EUREC/Hospices Civils de Lyon, France

Dr Octavi Quintana-Trías – European Commission, DG Research

# EUROPEAN COMMISSION-EMEA CONFERENCE ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE AND PERSPECTIVES FOR THE FUTURE

Thomas Lönngren, EMEA

3 October 2007

# Why do we have this conference?

- Experience shows some problems related to the implementation of the clinical trials directive
- Feedback from all parties
- Need to find a way forward
- Commission and EMEA offer an opportunity for discussion to all interested parties

# What are the Conference objectives?

- Implementation of the clinical trials directive
- Overview of experience to date
- Recommendations for the future

# Who are the partners involved?

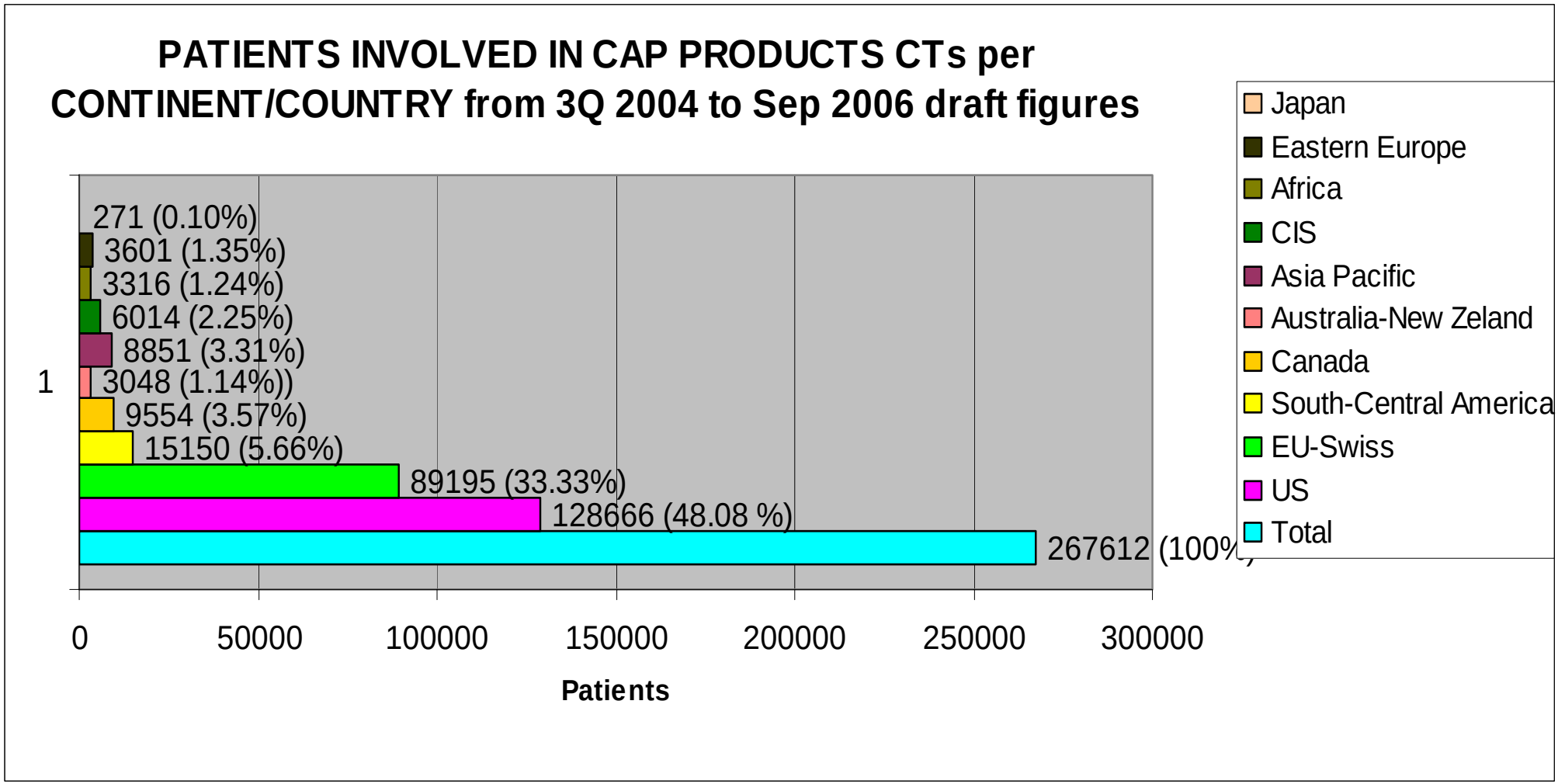
- European Commission
- National competent authorities
- Sponsors (commercial/non-commercial) and CROs
- Investigators
- Patients' representatives
- Ethics committees
- EMEA

# Some questions and assumptions

- We want clinical trials in the EU
- We want to have high quality clinical research and drug development in the EU
- What is the trend?
- To what extent the clinical trials directive is part of the trend?

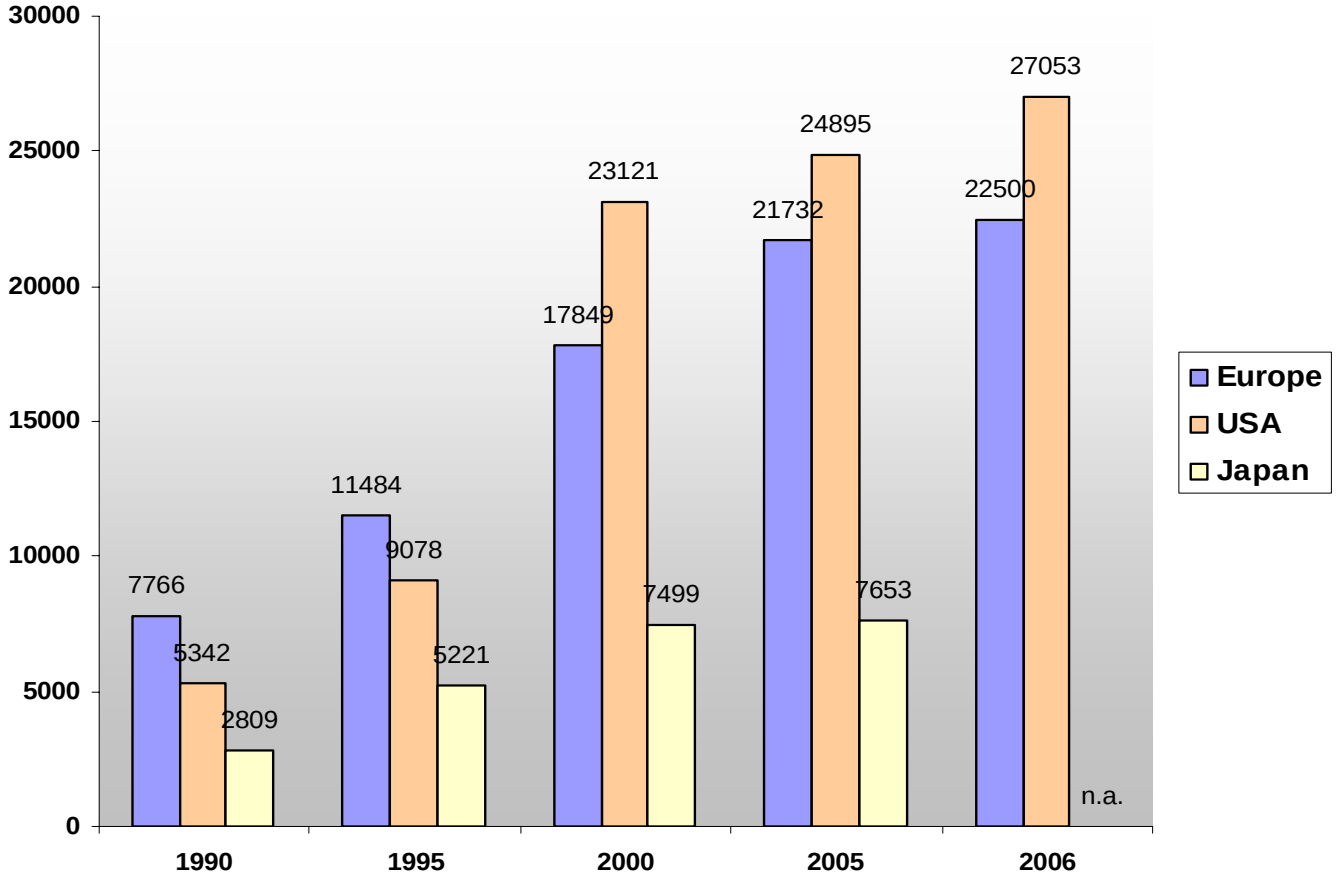

**27 EU Member States**
**+ 3 EEA**
**=**
**500 million people/**
**potential patients/**
**potential trials**
**subjects**


# Pivotal Clinical Trials in MAAs to the Centralised Procedure



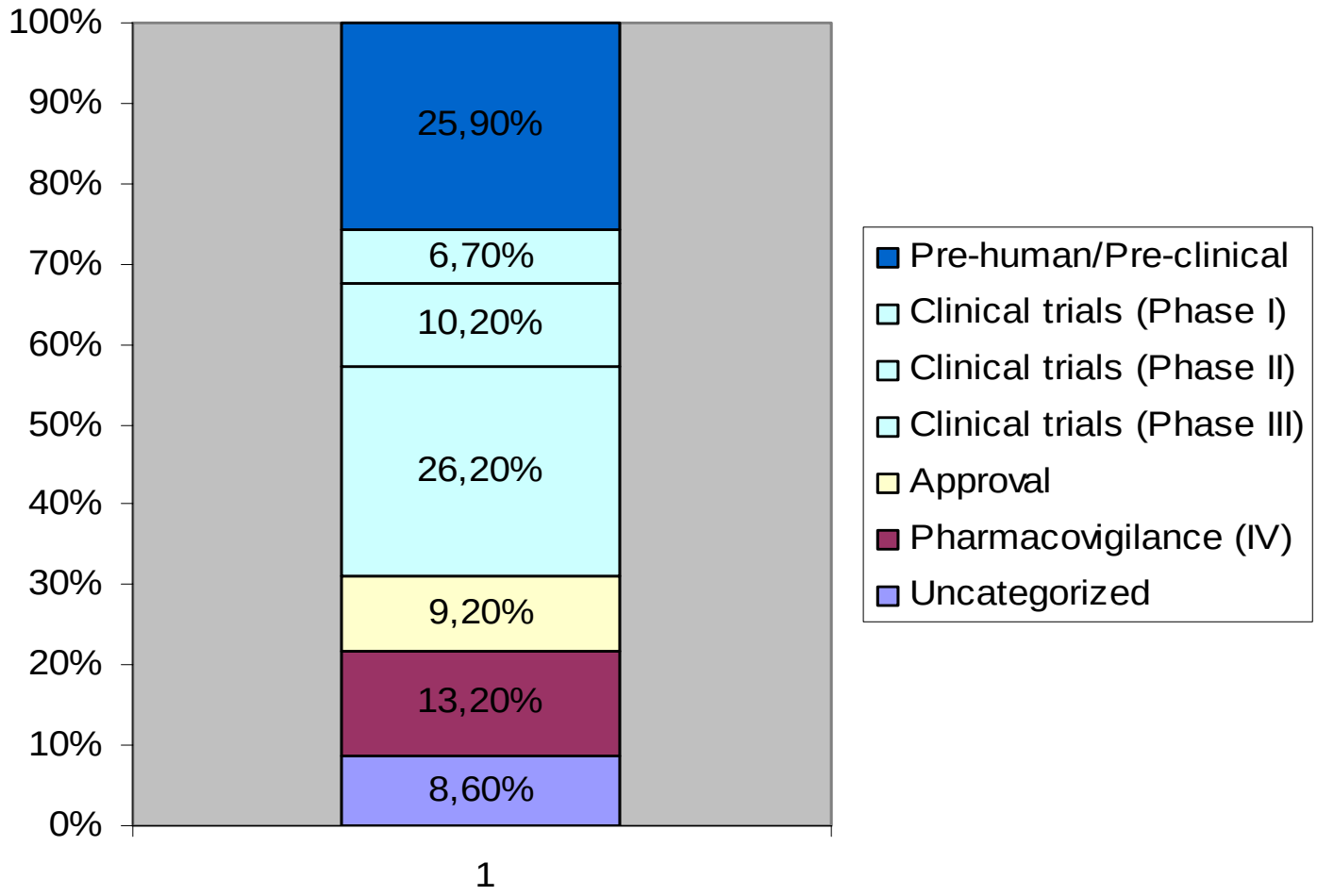
# Pharmaceutical R&D expenditure in Europe, USA and Japan, 1990-2006

## € million, current exchange rates



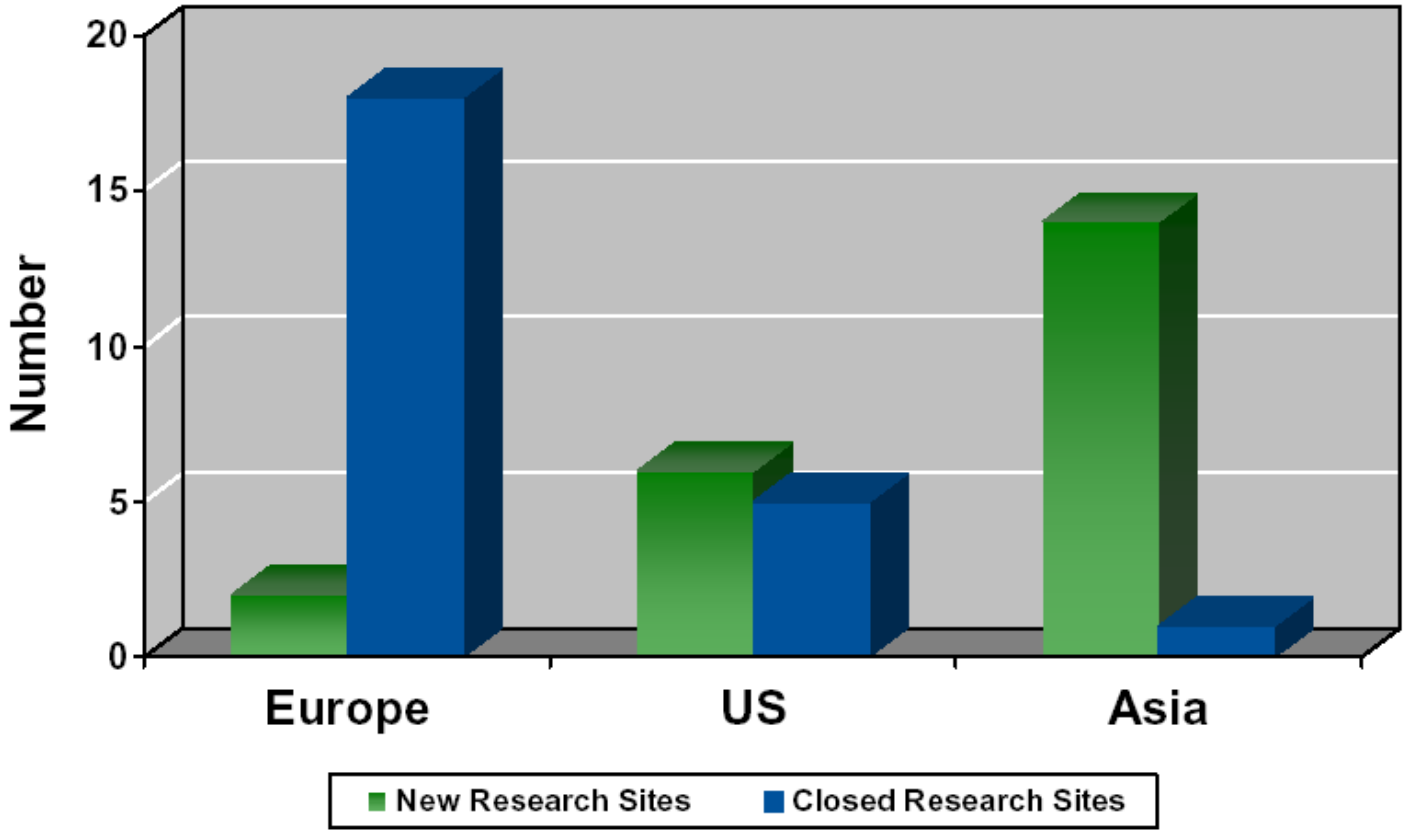

Source: EFPIA member associations, P*h*RMA, JPMA

# Allocation of R&D investments by function




Source: P*h*RMA, Annual Membership Survey 2006 (percentages calculated from 2004 data)

# Changes in Research Sites (2001 – 2006)



# What are the challenges?

- Globalisation of clinical research
- EU share of global research
- EU to ensure that the environment is favourable for clinical research

# Current legal framework

- Clinical trials in Europe
  - Directive 2001/20/EC
  - Directives 2005/28/EC and 2003/94/EC for GCP and GMP
  - EudraLex Volume 10
- Marketing authorisations in Europe
  - Regulation (EC) No 726/2004
  - Directive 2001/83/EC

# Objectives of clinical trial legislation

- Protection of subjects participating in clinical trials (EU and third countries)
- Ensure framework for high quality research in EU and its acceptability worldwide (product development, product authorisation)
- Promote a favourable research environment (clear and efficient administrative/scientific procedures)

**WHAT COULD WE DO IN ORDER TO SUPPORT THOSE OBJECTIVES?**

# Numbers of clinical trials registered in EudraCT (1 May 2004 to 1 August 2007)

Distinct clinical trials – 12.122 composed of:

- Clinical trial applications: **22.697**
- Type of sponsor
  - **Commercial sponsor: 18.319 (80,7%)**
  - **Non-commercial sponsor: 4.470 (19,7%)**
- Sites
  - **Single site: 6.412 (28,2%)**
  - **Multiple site: 15.017 (66,2%)**
- Countries
  - **Multiple member state: 13.652 (60,1%)**
  - **Including third country sites: 11.392 (50,2%)**

# MAIN QUESTIONS FOR THE CONFERENCE

- What works well?
- What does not work well?
  - What can be remedied within the current legal framework?
  - What requires changes to the legal framework?
- What are possible ways foreword:
  - Revised guidelines?
  - New legal framework?
- What are the issues for clinical trials in third countries?

Thank you

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

Alan Morrison, Vice-President International Regulatory and Safety, Amgen

## What aspects of the Directive 2001/20/EC and its implementing rules work well?

- The aim and spirit of the Directive provides the basis for:
  - Standardisation of the review processes and documentation
  - Parallel review by Competent Authority (CA) and Ethics Committee (EC)
  - Improving EC review process
  - Clear and consistent approval timelines
- But the potential benefits have not yet been realised

## Key areas in which action is required

- There is an urgent need to address fundamental issues with regard to:
  - Definitions
  - CTA applications
  - GMP requirements for IMPs
  - CA and EC review processes

- Facilitate harmonisation and provide clarity regarding requirements

- Make the EU a more competitive environment for clinical research and optimise access by EU patients to innovative medicines

# Definitions

- Investigational Medicinal Product (IMP)
  - Concept of a Non-IMP introduced with no legislative basis
  - Different interpretation of IMP definition by Member States (MSs)
  - Clear guidance and pan-European agreement essential

- Substantial and non-substantial amendments
  - Consistency across MSs in interpretation of ‘substantial’
  - Further guidance welcomed, including the process for notification
  - Clarification whether CA and/or EC approval is required

## CTA Applications

- Lack of harmonisation regarding information to be provided in CTA application
- Transparency in MSs requirements – published in Commission guidance and objectively justified
- Transparency of CA and EC approval timelines
- Provision of pan-European training for assesors to facilitate consistency in approach
- One CTA with harmonised requirements for all MSs
- Single submission point through EudraCT portal

## GMP requirements for IMPs

- A key area where harmonisation of requirements across EU MSs is imperative
  - Scope of IMP Manufacturing Licence
  - IMP labelling requirements

- MSs impose unreasonable requirements above those stated in the Directive
  - QP declaration not accepted by all MSs as assurance of GMP compliance for third country manufacturers

- Involvement of EMEA GMP Inspectors WG to address these issues

## CA Processes

- The Directive sets out timelines which have provided greater predictability
- Current process would be improved if all MSs undertook parallel CA and EC review of CTA applications
- Introducing mutual recognition of CA assessment
- Strengthening role of CTFG
  - Co-ordinate the CA review process
  - Arbitrate between MSs
  - Create process for sponsors to appeal MS decisions

## EC Processes

- Adoption of a single EC opinion per MS
- Clarity on scope of responsibilities of central ECs versus local ECs
- A common application form for all ECs would be welcomed

## Concluding remarks

- EuropaBio believe a revision of Directive 2001/20/EC and MSs legislation is necessary
- The aim of which would be to achieve greater harmonisation, transparency and consistency in approach across the EU
- This would further faciliate efficient development of all medicinal products, including biopharmaceuticals
- Support improved access by EU patients to innovative medicines

# Thank you

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

**Dr Monique Podoor, MD**

**Director EORTC Data Center**

**Please note that these presentation slides will be included in appendix to the report of the meeting and published at the same time.**

# What aspects of the Directive 2001/20/EC and its implementing rules work well?

- Resulted in partial harmonisation
- Unique identifier for trials
- Single EC opinion
- Triggered local investment in infrastructure & training
- Increased awareness and improved GCP compliance

# What does not work well?

- Transposition led to inefficient harmonisation at MS level
  - Disharmony at CA and EC levels across MS
    - Complexity of multinational trials
    - Increased administrative workload
    - Increased costs

# What does not work well? (cont'd)

- Not tailored for non-commercial research
  - Scope
    - Only trials with IMP
    - Not harmonised ( ex BE)
  - Definitions
    - Non-commercial sponsor vs. trial
    - Interventional / non-interventional / diagnostic
    - No risk-driven definitions & requirements
    - IMP definition
      - Pre vs. post registration
      - GMP requirements
      - Safety reporting requirements
  - Obligation of single sponsorship
    - Collaborative Intergroup trials

# What can be remedied within the present legal framework?

- Interaction between CA and EC
  - One stop-shop system
- Safety reporting requirements
  - Only one reporting entrance into the system
- Information on national requirements
  - Single integrated centrally managed database in English
  - Central helpdesk
  - Standardized electronic submissions to EC and CAs

# What can be remedied within the present legal framework? (cont'd)

- Clarity on definitions
  - IMP definition in different settings
  - Substantial amendments
- Redefining GMP requirements for advanced therapies
- Need for education / accreditation of ECs, investigators & staff

# What should a new legal framework look like?

- Single and comprehensive EU legislation
  - Cover all types of clinical research
- Facilitate high-quality clinical science
  - Central support for non-commercial sponsors
  - Involvement of all players
- Protect the trial participants
  - Risk-driven requirements

# What should a new legal framework look like?

- Centralized approval system
- Harmonized EC / CA interaction
- Accreditation for EC's and investigators
- Trial registry publicly accessible | data repository

Thank you

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

## Heads of Medicines Agencies
## Clinical Trial Facilitation Group (CTFG)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# What aspects of the Directive 2001/20/EC and its implementing rules work well?

- Scope of legislation
- Definitions
- Clinical Trial Authorisation and IMP Dossier
  - To Competent Authority
- IMP related issues (definitions, labelling, GMP etc)
- Competent authority processes
- Roles of ECs and NCAs

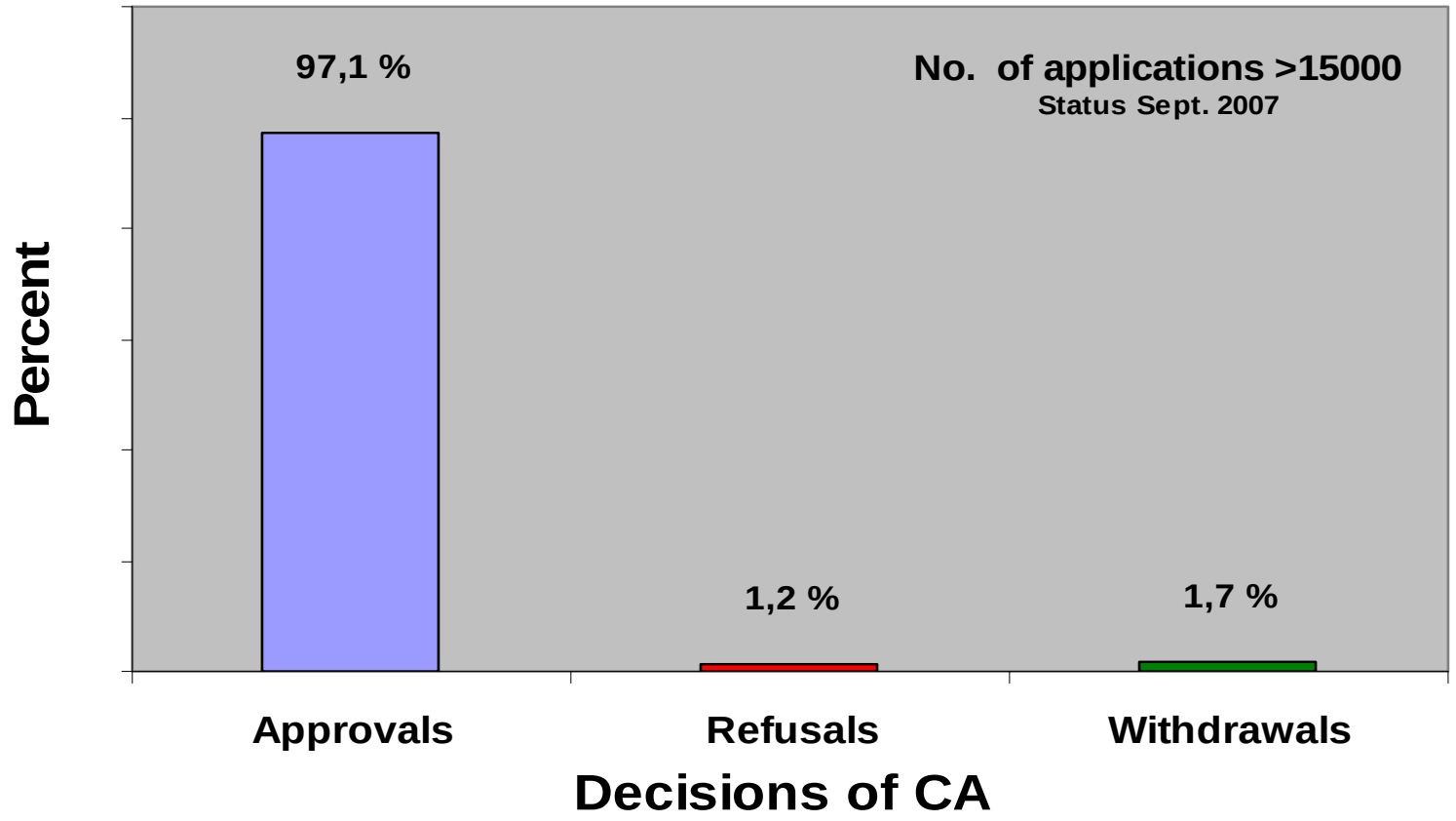
# What aspects of the Directive 2001/20/EC and its implementing rules work well?

| | |
|---|---|
| **Scope of legislation**<br>Article 1 (1-4) | 1.Specific provisions regarding the conduct of clinical trials<br>2.All clinical trials, shall be designed, conducted and reported in accordance with the principles of good clinical practice. |
| **Definitions** Article 2<br>▪ clinical trial / multi-centre clinical trial<br>▪ non-interventional trial<br>▪ investigational medicinal product<br>▪ sponsor<br>▪ investigator<br>▪ investigator's brochure<br>▪ protocol<br>▪ subject<br>▪ informed consent<br>▪ ethics committee<br>▪ inspection<br>▪ adverse event<br>▪ adverse reaction '<br>▪ serious adverse event or serious adverse reaction<br>▪ unexpected adverse reaction | **Additional guidance given in guidelines under:**<br>**EUDRALEX Volume 10 - Clinical trials** chapters 1- 5 e.g.:<br><br>ENTR CT 1<br>**- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial** October 2005 Revision 2<br><br>**- Chapter III : Information on the Quality of the Investigational Medicinal Product**<br>**- Recommendation on inspections**<br>- Guidance on IMP and other MP used in CTs (May 2007)<br><br>ENTR CT 3<br>**- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use** April 2006 Revision 2 |

# What aspects of the Directive 2001/20/EC and its implementing rules work well?

| | |
|---|---|
| **Clinical Trial Authorisation(CTA) and IMP Dossier** | - Approval required from EC and CA<br>- Content of the application for CTA and IMP-Dossier defined in guidance documents<br>- Transparent time lines for approvals<br>- defining specific conditions for CTA for biological products/GMO |
| **IMP related issues (definitions, labelling, GMP etc)** | - IMP dossier usable in several MS for multinational trials / Common requirements for IMP dossier as defined in Guidance CT1<br>- transparent MS specific requirements as defined in CT1 Attachment 1<br>- additional guidance given Vol 10 Chapter III : Information on the Quality of the Investigational Medicinal Product |
| **Competent authority processes** | - transparent timelines / dossier requirements<br>- deficiencies of applications (formal and scientific) will be communicated in writing<br>- Possibility to amend the content of the application when grounds for non-acceptance are given |
| **Roles of ECs and NCAs** | - Defined responsibilities of CA and EC<br>- EC and CA can work in parallel<br>- single opinion per MS |

# What aspects of the Directive 2001/20/EC and its implementing rules work well?



# What does not work well?
# But can be remedied within the present legal framework

| Topics/Problems | Suggestions |
|---|---|
| **Scope of legislation**<br>No problems seen by CTFG | No suggestions |
| **Definitions**<br>- Non IMP<br>- Definition of Non-IMPs and back-ground treatments are divergent in MS (particularly because of divergent status of NIMP (with MA in the MS concerned or not))<br><br>- Different understanding of Non-interventional-studies in different MS | - Further harmonisation in the ad hoc Group 2001/20 EC of examples given by applicants<br><br>- Guidance on definition of IMP and NIMP published by Commission;<br>- update of EudraCT Database to address NIMPs<br><br>- diagnostic or monitoring procedures are not the same in all MS, and one specific study could be considered a non interventional study in some MS and a CT in others ➔**discussion of diverging decisions between MSs and in <u>CTFG</u>** |
| **Clinical Trial Authorisation and IMP Dossier**<br>- additional national requirements for CTA<br><br>- diverging decisions of MS on the same CTA | - regular update of Attachment 1 of ENTR CT1<br>- development of harmonised documents with core requirements by **<u>CTFG applications subgroup</u>**<br>- sponsor discuss critical issues with concerned MS before CTA (“advice Meeting” via written procedure and/or teleconference and/or “breakout session” during CTFG meeting<br><br>- develop a suggestion for sharing assessments by **<u>CTFG scientific harmonisation subgroup</u>**<br>- discussion of diverging decisions between MSs and in **<u>CTFG</u>** after or during CTA |

# What does not work well?
## But can be remedied within the present legal framework

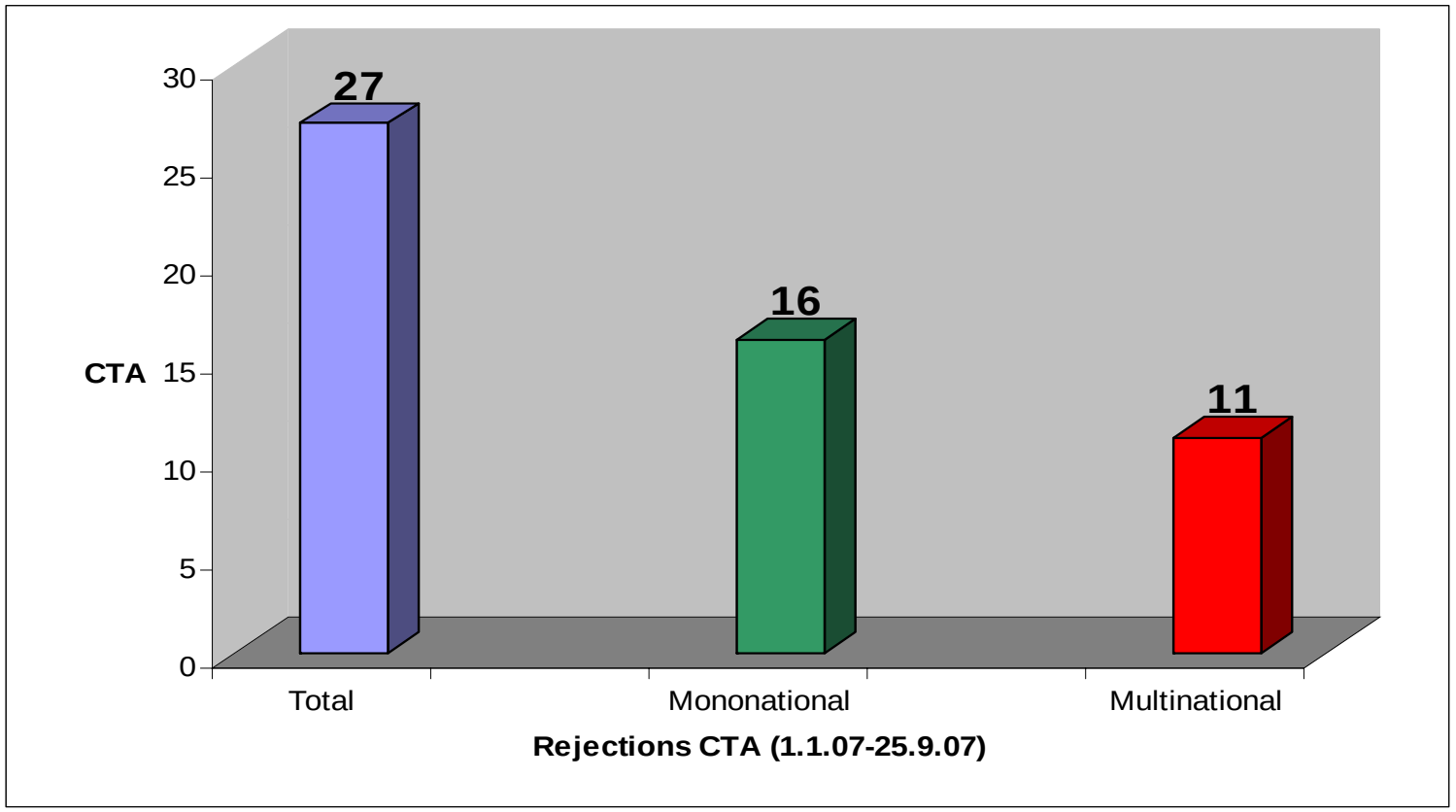
| Topics / Problems | Suggestions |
|---|---|
| **IMP related issues (definitions, labelling, GMP etc)**<br>- Lack of clarity or agreement on role and responsibility of QP in releasing clinical trial<br>- GMP documentation for third country manufacturing<br>- Different labelling requirements | **meeting / discussion according EFPIA proposal with *European Commission, the Clinical Trials Facilitation Group, the EMEA GMP Inspection Services working group on a harmonised understanding of GMP requirements for IMPs*** |
| **Competent authority processes**<br><br>- diverging decisions of MS on the same CTA | - discussion of critical issues **before CTA** with concerned MS ("advice Meeting" via written procedure and/or teleconference and/or "breakout session" during CTFG meeting<br><br>- develop a suggestion for sharing assessments by **CTFG scientific harmonisation subgroup**<br>- discussion of diverging decisions between MSs and in **CTFG** after or during CTA |
| **Roles of ECs and NCAs**<br>- EC and CA do not work in parallel but EC vote is pre-requisite for CTA | - discussion of topic in 2001/20/EC ad hoc group after the details by sponsors and MS are given<br>- further clarification in guidance documents |

# What does not work well?
## But can be remedied within the present legal framework

| Topics / Problems | Suggestions |
|---|---|
| **Competent authority processes**<br><br>- diverging decisions of MS on the same Clinical Trial Application<br><br>- Different time lines between the MS | - discussion of critical issues **before CTA** with concerned MS ("advice Meeting" via written procedure and/or teleconference and/or "breakout session" during CTFG meeting<br><br>- harmonised procedures and sharing of assessments by **MS and/or CTFG scientific harmonisation subgroup**<br><br>- **implementation of voluntary harmonised CTA**<br>  - **Harmonised start of CTA or Amendment submission**<br>  - **Consolidated list of Questions (GNA) for CTA**<br>  - **Consolidated opinion of MS**<br>  - **Approval according national regulations** |

# What can be remedied within the present legal framework? Topics of Harmonisation

Rejections of CTA submitted between 1.1. -25.9.2007
2-8 MS in the 11 multi-national trials (no unanimous decision)



# What can be remedied within the present legal framework? Topics of Harmonisation

## FIM Studies

Status 3.4.2007

| | |
|---|---|
| Total | 784 |
| Mono-national | 680 |
| Multi-national | 38 (2-11) |

# What should a new legal framework look like?

Is a new legal framework needed to address the mentioned problems?

Presently, CTFG sees no need for a new legal framework, but is open to learn from you!

# Summary

- Major advances in the approvals of multi-/ national CT have been reached by 2001/20/EC
- Further harmonisation of documentation (IMPD etc) is possible and under way
- Further harmonisation of scientific assessments and decisions of multi-national CT is needed, but achievable within the current legal framework (e.g. CTFG)

# Thank you

IWE Institut für Wissenschaft und Ethik

# European Commission – EMEA Conference on the Operation of the Clinical Trials Directive and Perspectives for the Future

**Michael Fuchs (Bonn)**

## The Implementation of the EC Directive 2001/20 and its Impact on the Work of Research Ethics Committees in Different European Countries

**London, October 3, 2007**

**Why are Ethics Committees in research on human subjects necessary?**

**Historical experiences show that human beings have been abused badly in medical research. Individuals have been sacrificed for scientific curiosity and/or for the benefit of society as a whole (e.g. Nazi experiments, the Tuskegee Syphilis Study, etc.).**

**The concept of Human Rights incorporates the rules not to harm people and to respect them as persons. In contrast, by using human beings as research subjects they may be treated as mere means.**

**Ethical scrutiny can be managed best by independent interdisciplinary committees.**

**Already before the European Directive on GCP was translated into national law the member states of the EU and those who became members meanwhile had some system of ethical regulation for clinical trials that defined the function of research ethics committees (RECs).**

**This means that member states already had „independent bodies“ „consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent“.**
**(Directive 2001/20/EC, Art. 2 (k))**

- **The results from a survey we prepared in 2003 for the EC showed that research ethics committees and their members felt committed to the same principles: Helsinki-Declaration, Oviedo-Convention**
- **Nobody indicated that a special philosophical or ethical tradition of a country or a region would be important or even binding for the work of the REC.**

- In those countries where no legal regulation for the work of RECs existed before committee members expressed the need of a clear and binding system.
- In those countries where the vote of the REC already represented a binding decision for the researchers  experts discussed the change in the role of RECs (judgement vs. advice) critically.

**The European Directive made obvious that it is an obligation of the state to ensure the functioning of a system of ethical evaluation and regulation:**

**„Article 6: Ethics Committee**

**For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees.**

**The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested.“**

**The Directive and its implementation did not change the status quo as far as membership of RECs is concerned.**

**Different structures may be in accordance with the Directive:**

- **A committee system with only one level has to be distinguished from a two level system.**
- **A single level system can be central (Slovenia) or local (Belgium) or regional (France).**
- **In a two level system the national or central level may take very different shapes:**
  - **function of a consultant (Committee at the German Federal Chamber of Physicians)**
  - **instance of appeal (Poland, Netherlands)**
  - **coordinating authority (Netherlands)**

**Where a central committee combines several functions this can mean an accumulation of power.**

**The Directive does not foresee any safegards against centralized power.**

**Nevertheless the obligation to translate the Directive into national law was a starting point for legislation and policy making in the member states that sometimes was not explicitely required and in some respects even took opposite directions:**

## Centralization

**Greece: The directive has been incorporated into Greek Law through Ministerial Decision DYC3/89292 and State Journal B' 1973/31.12.2003. This implementation created a National Committee which takes the final decision regarding research projects.**

**Portugal: Law 46/2004 (19th August) implements the Directive. It has introduced several changes in the system of ethical review. An opinion is now required from the newly created central ethics committee; the central committee is allowed to ask a local committee to fulfil this task.**

## Decentralization

**Slovenia: The Slovenian Directive on Clinical Drug Testing is based on the European Directive.**

**There is a certain move towards decentralisation, local RECs are empowered to take up part of the responsibilities of the National Medical Ethics Committee.**

## Creation of an instance of appeal

**Ireland: An appeal can be made to the Ethics Committees Supervisory Body for a second REC opinion or against the original REC decision. The 1987 &1990 Acts stipulate that no legal action can be taken against an REC. There is provision for clinical indemnity for all members of ethics committees in the Department of Health guidance.**

## Creation of a state agency for drugs

**Lithuania: This was implemented through a Ministry of Health Decree of 11 May 2004. The most significant change in the system was that approval from the State Drug Control Agency is required for clinical trials on medicinal products in addition to a positive opinion from an REC.**

## Legal strengthening of the REC opinions

**Italy: The directive has been implemented through Legislative Decree no. 211 of 24 June 2003. The RECs have now the power to give a legally binding opinion to a research protocol.**

**Spain: The directive was implemented by Royal Decree 223/2004, Article 60, 62 and 65 of Law 25/1990. It will affect protocols of tests involving minors or incapacitated adults, where expert advice will be required by RECs. It will also require follow-up procedures for protocols receiving a positive opinion.**

**Belgium: The law implementing the Directive came into force on 7 May 2004. RECs now have a legal status and evaluate protocols according to defined criteria.**

## Only slight changes

**The Netherlands: There have been slight changes regarding the criteria and organisation of the review with the new law which came into force on 1 March 2006.**

**Sweden: Modifications concerning clinical trials where minors and incapacitated adults are involved; single opinion for multi-centres trials; time frame for ethics review; particular expertise in the RECs.**

**Poland: The directive was implemented in the legislation of 2002. Ministry of Health Act Nr.221 poz.1864.**

**Latvia: Addition to the Pharmacy law: 20.08.02 and amendment (30.04.04) to the Cabinet Regulations no.312.**

**The directive has been implemented by the 12th amendment of the Medicinal Drugs Act which came into force in August 2004.**

- **The implementation introduced European regulations on pharmacovigilance and the good clinical practice standards.**
- **The amendment stipulates that only the REC under public law, not the ‚free' RECs, may assess clinical drug trials.**
- **Ethics committees under public law have adjusted variably quickly to changing prevailing conditions after implementation of the European directive. Partly they stress increased bureaucratic burden and complication of the legal situation.**

## Continuing problems

- Despite the legal and institutional requirements it is not always easy to find experts willing to do the work.
- In different European regions there are difficulties to find trained lawyers.
- In some Central and Eastern European countries there are not enough philosophers familiar with the field of biomedicine.
- The absence of members is still a problem (cf. Huriet 2001, national report France for EULABOR 2006).
- The Directive does not provide a legal framework to conduct research in situations of emergency (c. CoE, Protocol on Biomedical Research, Art. 19)

## Conclusions

**A review of the process of implementation reveals several aspects that are somewhat problematic.**

**To successfully accomplish the task of reviewing all research projects necessitates a working and well funded committee.**

**Especially in some eastern European countries a lack of funding for those committees may endanger the functionality of the committees and make compliance with the 60 day limit (Directive 2001/20/EC, Art. 6, (5)) a difficult task to say the least.**

## Support and Sources

- Martin Heyer – Legal data collection and analysis
- Country information by partners from EUREC
- Bert Heinrichs: Forschung am Menschen. Elemente einer ethischen Theorie biomedizinischer Humanexperimente, Berlin/New York 2006 (= Studien zu Wissenschaft und Ethik 3)
- http://www.eurecnet.org
- http://www.privireal.group.shef.ac.uk

**Thank you**

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

Fernand Sauer
Honorary Director General of the European Commission

# Clinical trials issues in Developing Countries

- Burden of poverty related diseases
- HIV/AIDS: 40 mio infected, 3 mio deaths/Year
- Malaria: 1/2 bio sick, 1 mio deaths/Year
- TB: widespread, 8 mio new, 2 mio deaths/Y
- Weakness of health systems & prevention
- Neglected diseases, no “orphan drugs”
- Lack or affordability of technologies
- Tropical diseases: 1% of all new drugs
- Some results with Leprosy, Trachoma…
- Some innovative interventions (Kangaroo)

# Criteria for clinical trials in Developing Countries

- Need to adjust clinical interventions tools
- Safe, effective, affordable, easy to apply
- Worldwide impact of EU/ICH harmonisation
- More influence of Dev. Countries on R&D
- Ethics, consent, cultural acceptance
- Opinion n° 17 of European Group on Ethics
- Capacity building, sites and training
- Continuity of access to treatment
- UN Millenium Goals, G8, Mexico Ministerial

# EDCTP
## European& Developing Countries Clinical Trials Partnership

- Set up in The Hague & Cape Town in 2003 between 15 Member States (Treaty ART 169)
- €200 million Budget support from EU/FP6
- In addition, €258 million for poverty diseases
- Overall goal: to reduce poverty in developing countries by improving the health of the populations
- EDCTP aims to develop new clinical interventions
- To fight HIV/AIDS, Malaria and Tuberculosis
- **Through North/South partnerships**
  - **Better European research integration**
  - **Sustainable partnership with African countries**

## EC has supported the request of a cost neutral extension of the Grant to 2010

**After a difficult start from 2003 to 2005, major efforts were undertaken since 2006 to improve the EDCTP performances**

EDCTP / Independent External Review Panel,
January to July 2007, See Report:
http://www.edctp.org/fileadmin/documents/Final_IER_report.pdf

# Funding of EDCT Program: neutral cost extension

**MS must match the EC contribution at the level of EDCTP funded projects as already foreseen in the last calls or by direct contributions**

**Cofunding as one of the instruments to achieve integration of National programmes**

**So far:**
**Only 35 of 200 million promised by Member States**
**Only 7 of €200 million expected from Third Parties**

# CHALLENGES FOR EDCTP

For EDCT to be supported under FP 7, beyond 2010:

- Get more results in the field of activities in Africa and in integrating National Programs,
- Generate a real joint program between MS
- Attract and mobilize EU pharmaceutical industry
- Ministers to renew EDCTP “vows” and to provide real fresh funds
- Establish ownership of the EDCTP by African countries (political, scientific and institutional)
- Develop specific EDCTP procedures for Intellectual Property Rights and Ethical Review

# Recommendations on clinical trials in Developing Countries

Review of Directives 2001/20/EC & 2005/28/EC:

- Evaluate and consolidate provisions protecting clinical trial subjects inside and outside the EU, avoiding clinical « dumping »
- Receive input from pharmaceutical companies and WHO/TDR involved in clinical trials in poor countries, trial registries public?

EMEA and Commission, towards EDCTP:

- Reinforce EU synergies DG RTD/DEV/SANCO & EMEA
- Art 58 type « scientific advice » to EDCTP and WHO ?

EU and Member States, towards Develop. Countries:

- Promote adaptation of ICH/EU GCP principles via WHO
- Help develop Ethics in Developing Countries
- Support capacity building in Developing Countries
- Increase support to non-commercial clinical research, i.e. EDCTP

Thank you

efpia

European Federation of Pharmaceutical Industries and Associations

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

# Safety Reporting

Gaby Danan MD , PhD

Sanofi-aventis

on behalf of EFPIA

# What aspects work well?

- Definition of SUSARs although….
  - No standard for ‘Important medical event’
  - No consistent reference for expectedness
- Reporting timelines: 7/15 days
- Electronic reporting using ICH E2B format
- Recognition of implementation problems
  - Agreement to work on improvements
- Recognition to ensure the safety of patients enrolled in clinical trials

# What does not work well? 1/3

1. SUSAR reporting to National Competent Authorities (NCA)
   - Variation between countries
     - SUSAR: local, within or outside the EEA, IMP, trials, indications,…
     - Unblinding rules

2. Annual Safety Report
   - Variation between countries
     - Serious Adverse Reactions Line listings and summary tables: Periodic or cumulative, local or global, by trial or all inclusive, blinded or unblinded,…

3. Electronic transmission to EudraVigilance
   - High duplication rate of case safety reports OR
   - No report at all
   - Data quality issues: e.g., no narrative, inconsistencies
   - IMP not identified

# What does not work well? 2/3

## 4. Communications to Ethics Committees

- Variation between countries
  - All SUSARs or local SUSARs
    - On paper or electronic format deviating from ICH E2B
  - Line listings or just a fraction with specific data
  - Expedited or periodic safety information
  - SUSARs from approved trials or any other trials involving the IMP
  - Fees!
  - ….

# What does not work well? 3/3

5. Communications to investigators (paper)
   - Variation between countries
     - Expedite all SUSARs
     - Expedite local SUSARs and Periodic Line Listings for foreign SUSARs
     - Periodic Line Listings only
     - Not specified

# What can be remedied within the present legal framework?

1. Electronic transmission of all SUSARs involving the IMP(s) to EudraVigilance
2. SUSAR Periodic (3 or 6-month) Line Listing and concise safety summary to Ethics Committees and investigators
   - Alternatively, EudraVigilance data via the NCA
3. Uniform Annual Safety Report in the EEA
4. Strengthen reporting rules to EudraVigilance
   - Data quality
   - Business rules

# What should a new legal framework look like?

1. Clear content and reporting rules of SUSARs and ASR
2. Clear reporting rules to Ethics Committees and investigators
3. Better use of EudraVigilance database
   - Common repository for SUSARs and SSARs to assist overall safety assessment of IMPs
4. Mandatory population of the EudraVigilance-Medicinal Product Dictionary (EV-MPD) with IMPs and full alignment with EudraCT IMP description
5. Work sharing for the SUSARs and ASRs assessment

Thank you

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

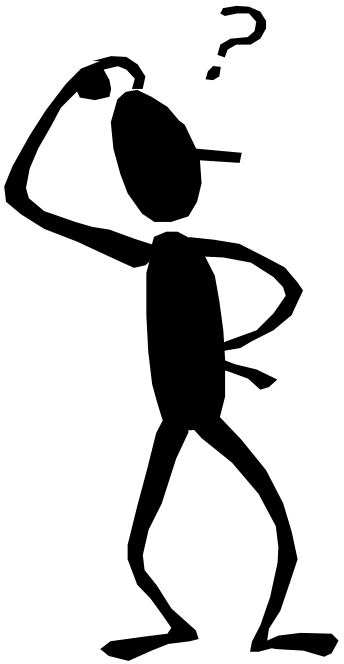
## SESSION 3

Stefan Bielack
Klinikum Stuttgart - Olgahospital
Pädiatrie 5
(Onkologie, Hämatologie, Immunologie)
Stuttgart, Germany
*coss@olgahospital-stuttgart.de*

L 121/34 EN Official Journal of the European Communities 1.5.2001

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 4 April 2001
on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

# What aspects of the Directive 2001/20/EC and its implementing rules work well?



News In-depth

## Clinical Trials Directive slows registration of paediatric studies

Registration of new non-commercial paediatric trials in Europe essential for optimising paediatric treatments—has fallen since the Clinical Trials Directive 2001/20/EC was implemented, according to sarcoma experts meeting in Stuttgart, Germany (Nov 30-Dec 2, 2006). "Before implementation, 10–20 studies were opened per year in the UK, but this has now fallen to just a handful", says Kathy Pritchard-Jones (Royal Marsden Hospital, London, UK). "Treatment within a trial is associated with definite survival advantage and, with fewer trials available, we must fear cure rates in Europe will decline as a direct consequence of legislation which was originally intended to protect patients", Stefan Bielack (Olgahospital, Stuttgart, Germany) told *The Lancet Oncology* (*TLO*).

For more information on the EURAMOS1 trial see http://www.euramos.org

Because the 2001 legislation was a directive it became mandatory for European Union member states to adopt the legislation by May 2004. The directive's aim was to simplify and harmonise administrative procedures governing trials and to provide patient protection by setting pan-European legal standards. However, although stakeholders were slow to react initially, there has been growing concern about how this legislation might hamper the running of non-commercial academic trials, particularly those in children. "Trials in children are particularly disadvantaged because these cancers are often complex heterogenous diseases requiring complex multimodal treatments, and are rare diseases requiring wider international collaboration", says Jeremy Whelan (University College Hospital, London, UK). Many trials in children try to optimise treatment rather than test new drugs. Bielack notes: "these treatments for children are not lucrative and nobody is willing to finance the extra costs or to assist in managing the exponentially increased bureaucratic workload". According to Herbert Jürgens, from the University Children's Hospital in Muenster, Germany, the Commission Directive 2005/28/EC set-out guidelines for good clinical practice and addressed some of these initial concerns, but this later directive did not exempt trials optimising treatments from full compliance with the 2001 directive. Another issue Bielack told delegates at the Stuttgart meeting that the directive requires a single sponsor to take overall responsibility for initiating and managing the trial, including all of the legal, ethical, and financial aspects, thereby taking on all the liability for no commercial benefit. Furthermore, Jürgens told *TLO* that: 50–90% of medicines have never been evaluated in children and are classified as investigational medicinal products (IMPs) because they are often used outside their marketing indications. "The need for trials in children to develop paediatric medicines is gaining global recognition to avoid such off-label use, with its associated potential for inappropriate dosing and unforeseen adverse drug reactions".

For more information on the European Science Foundation see http://www.esf.org

In any trial, the sponsor has to report suspected unexpected serious adverse reactions (SUSARs) associated with IMPs to the competent authority, to the ethics committee, and to all investigators within 15 days of knowledge of a non-fatal event. But in Germany, Bielack commented, another level of bureaucracy has been added: "the same reporting requirements are mandatory for SUSARs from other studies investigating the same IMP". He cites as an example the use of interferon in the EURAMOS1 trial—a multinational collaborative study in children with osteosarcoma, launched under the new directive, of which he is the co-ordinator. "Interferon is used in a multitude of completely unrelated diseases and in adults [including] elderly patients with significant comorbidity. From the experience of the first 10 months of our trial, we have extrapolated that 180 000 pages of often irrelevant information on SUSARs will be distributed throughout Germany. This is like a polymerase chain reaction for waste paper and is bound to lead to a desensitisation for any real toxic-effects data."

Nonetheless, those at the Stuttgart meeting acknowledged the directive has resulted in a better structuring of multinational trials, and they highlighted the success of EURAMOS1. According to Mariana Resnicoff (co-ordinator of the European Science Foundation's European Collaborative Research Programme on pan-European Clinical Trials that provided funding for EURAMOS), "the experience gathered by the EURAMOS investigators could serve to pave the way for future pan-European academic clinical trials". Bielack agrees: "the EURAMOS group has developed strategies to deal with issues such as sponsorship and pharmacovigilance that might be applied to other trials and a single European safety desk for paediatric oncology trials should be considered".

To help future trials in Europe, the European Medical Research Councils are participating in a consultation initiated by the European Commission–Directorate General Enterprise and Industry on a paper *Draft guidance on specific modalities for non-commercial trials*, which is due to be released for comment in June 2006.

*Emma Cannell*

Money is not available for trials in children



NEWS

**Tied up in red tape, European trials shut down**

## TRIAL AND ERROR

**The European Clinical Trials Directive has created bureaucratic nightmares and is shutting down trials. Since the directive's launch:**

| | |
|---|---|
| Increase in the cost of academic cancer trials in the UK | 200% |
| Drop in academic drug trials in Finland | 75% |
| Drop in academic trial submissions in Ireland | 70% |
| Increase in the cost of trials supported by EORTC | 85% |
| New trials supported in 2004 by the group | 19 |
| New trials supported in 2005 by the group | 7 |

Sources: Cancer Research UK; *Brit. Med. J.*; EORTC

# What aspects of the Directive 2001/20/EC and its implementing rules work well?

**Dossier maintenance including substantial amendments**
**- content defined**

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

**a) Expedited reports**
**- clear definitions, clear responsibilities, possibilitiy to exempt**

**b) Annual safety reports**
**- rather unproblematic**

**Databases: EudraCT, EudraVigilance**
**- in place**

**Inspection (GCP, GMP)**
**- (fortunately) no personal experience**

# What does not work well?

**Dossier maintenance including substantial amendments**

**- no clearcut definition of “substantial”**

**- too much paper, center to center & intracenter redundancy**

# Documentation to be held by investigator / institution for clinical trials

**Detailed guidance for the principles of GCP in the conduct in the EU of clinical trials on medicinal products for human use. ENTR/6416/01, July 2002**

- Investigators brochure (+ updates) or SmPC
- Protocol and amendments (signed)
- Information sheet and consent form (+ updates)
- Financial aspects
- Insurance statements
- Signed agreements between parties
- EC opinion and composition
- MRHA authorisation
- Investigators CVs
- Medical and laboratory tests, including normal ranges
- Medicine labels
- Instructions for medicine use
- Shipping records
- Certificates of analysis
- Decoding procedures
- Master randomisation list
- Monitoring reports (pre-trial, initiation, close-out etc)
- List of persons responsibilities delegated to (+ updates)
- CRFs and corrections
- SAE notifications from investigators and to EC and MRHA
- EC/MRHA annual reports and final reports
- Subject screening log
- Subject identification code list
- Subject enrolment log
- IMP accountability at site
- Record of retained tissues
- Documentation of IMP destruction
- Completed subject identification code list
- Audit certificate
- Clinical study report


# Documentation to be held by investigator / institution for clinical trials

**Detailed guidance for the principles of GCP in the conduct in the EU of clinical trials on medicinal products for human use. ENTR/6416/01, July 2002**

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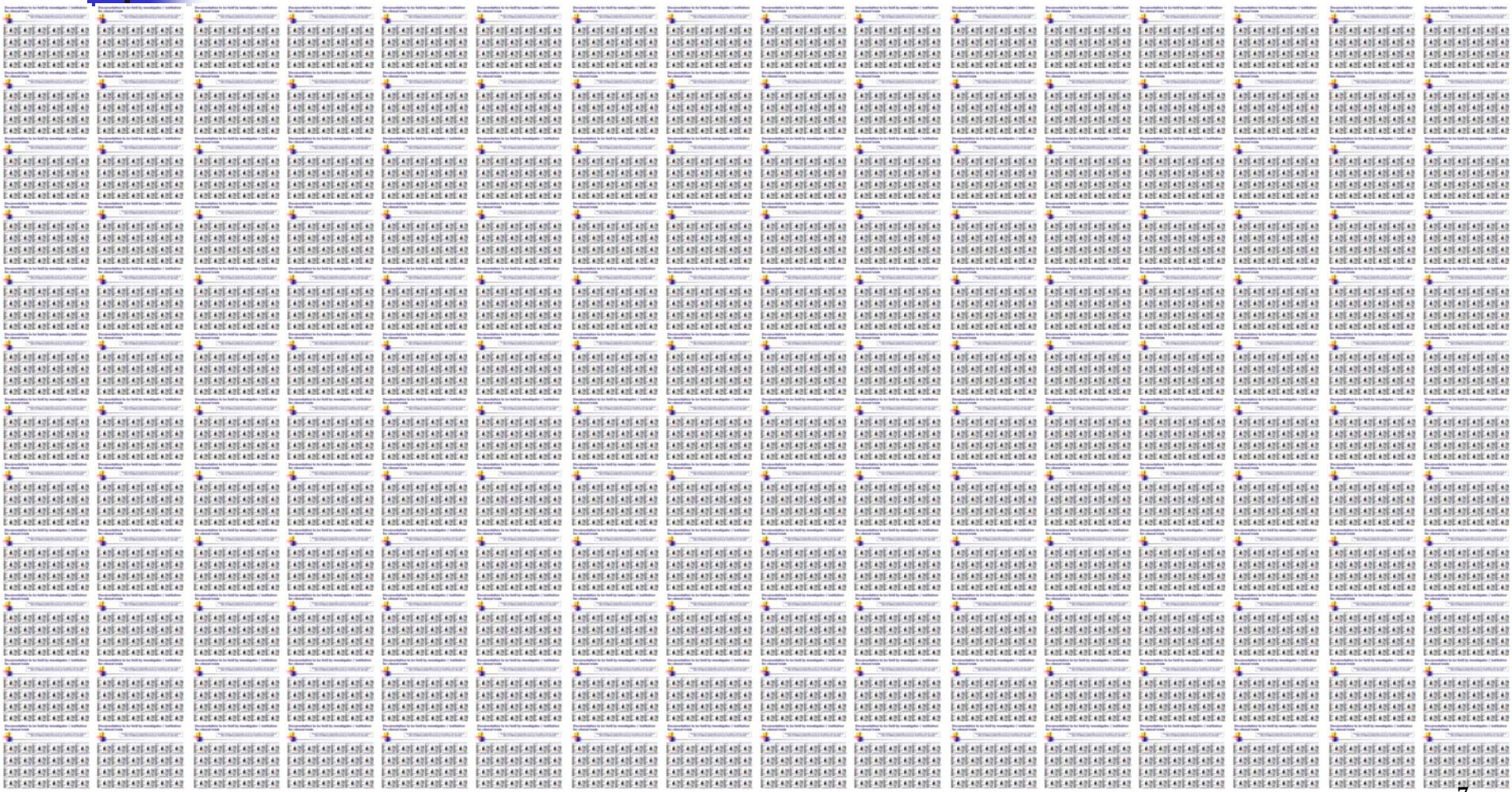


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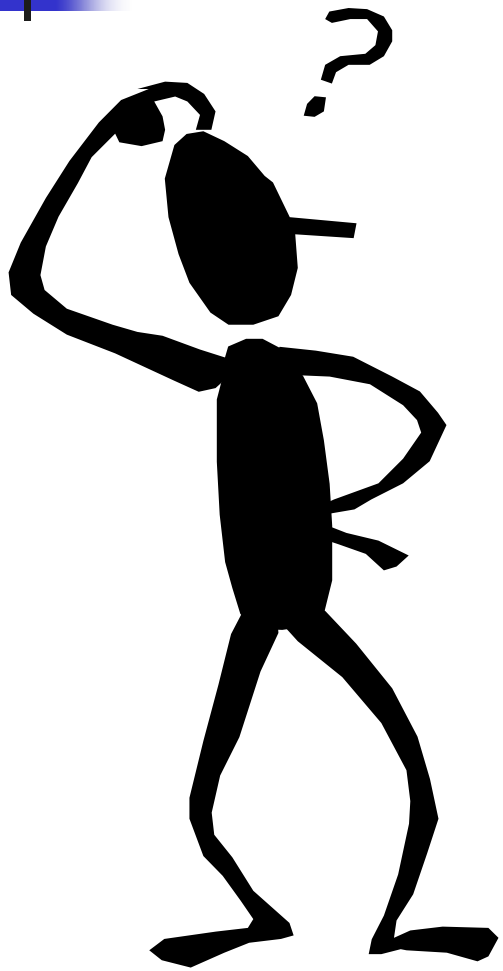


# What does not work well?

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

**- unbelievably & unneccessarily complex for multinational trials**

**a) Expedited reports**

**- multiple national submissions, diverse formats & procedures**

**- no check for content, too many recipients, national peculiarities**

**=> too much garbage to too many recipients**

330.000
pages


Thanks to Ewa Koscielniak for the idea

# What does not work well?

**Safety information, collection, reporting and review of safety information**
**b) Annual safety reports**

**- is all of the content really necessary for licensed drugs with known safety profiles?**

**Databases: EudraCT, EudraVigilance**

**- why are these additional requirements & not the only sites to report to???**

**Inspection (GCP, GMP)**

**- who pays?**

# What can be remedied within the present legal framework?

**Dossier maintenance including substantial amendments**

**- uniform European definition for "substantial" amendments**

**- cut down redundant paperload** (e.g.1 "site file" for all trials complemented by smaller ISFs)

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

**- to only one European address in one Pan-European format**

**- only annual reports & safety concerns to all investigators (not all SUSARS)**

**Databases: EudraCT, EudraVigilance**

**- delete other reporting obligations**

**Inspection (GCP, GMP)**

**- reduce cost**

# What can be remedied within the present legal framework?

- **less waste-paper production**
- **less € wasted**
- **less time spent on nonsense**
- **more time for patients**
- **more resources for science**

# What should a new legal framework look like?

- **harmonize the current dysharmony**
- **reduce multiple redundant national tasks, use central infrastructures**
- **cut down national extra-requirements**

# Thank you

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

# Conduct of Trials

Clinical Trials Facilitation Group
Brian Davis MHRA

# What aspects of the Directive 2001/20/EC and its implementing rules work well?

- **Conduct of trials:**
  - **Risk based approach to reporting;**
  - **Modification of guidance;**
  - **ASR - IBD for marketed products;**
  - **Electronic reporting available;**
  - **EudraCT information and alerts;**
  - **Eudravigilance for safety reports.**

# What does not work well?

- Identification of substantial amendments;
- Identification of SUSARs;
- Electronic SUSAR reporting not used;
- MS differences for ASR;
- EudraCT information not up to date;
- Eudravigilance data can’t be analysed.

# What can be remedied within the present legal framework?

- CTFG - harmonised approach and guidance:
  - Substantial amendments;
  - SUSAR and ASR reports;
  - Electronic reporting;
- Commission - additional clarification;
  - Definition of IMP;
  - Non commercial trials;
  - FIM trials.
- EMEA: Safety data analysis.

# What should a new legal framework look like?

- **No change:**
  - **Substantial amendments;**
  - **End of trial;**
  - **Eudra Databases;**
- **Change:**
  - **Mandate for electronic SUSAR reports;**
  - **Modify requirements relating to ethics committees.**

# Thank you

# THE CLINICAL TRIALS DIRECTIVE (Directive 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

**Pierre Henri BERTOYE (Afssaps, France)**
**on behalf of the**
**GCP Inspectors Working Group**

**V.7, 28/09/2007**

# Plan of the presentation

1. Reference texts for GCP
2. Implementation of National systems for GCP Inspections
3. Cooperation between MS and EMEA
4. Quality and harmonisation of inspections
5. Inspection results: reporting and tranparency

# GCP inspections

## 1. Reference texts for GCP

**ICH GCP**: Internationally agreed reference standard,

Developped by 3 ICH regions in the context of Marketing autorisation

« Clinical trial data that are intended to be submitted to regulatory authorities »

- Not referred to in the Directive 2001/20/EC; only « to be taken into account » in a « Recital » of Directive 2005/28/EC
- Common principles for all trials but some details may be interpreted / adapted for some clinical trials with specific characteristics

**Implementation of ICH GCP not harmonized between MS**

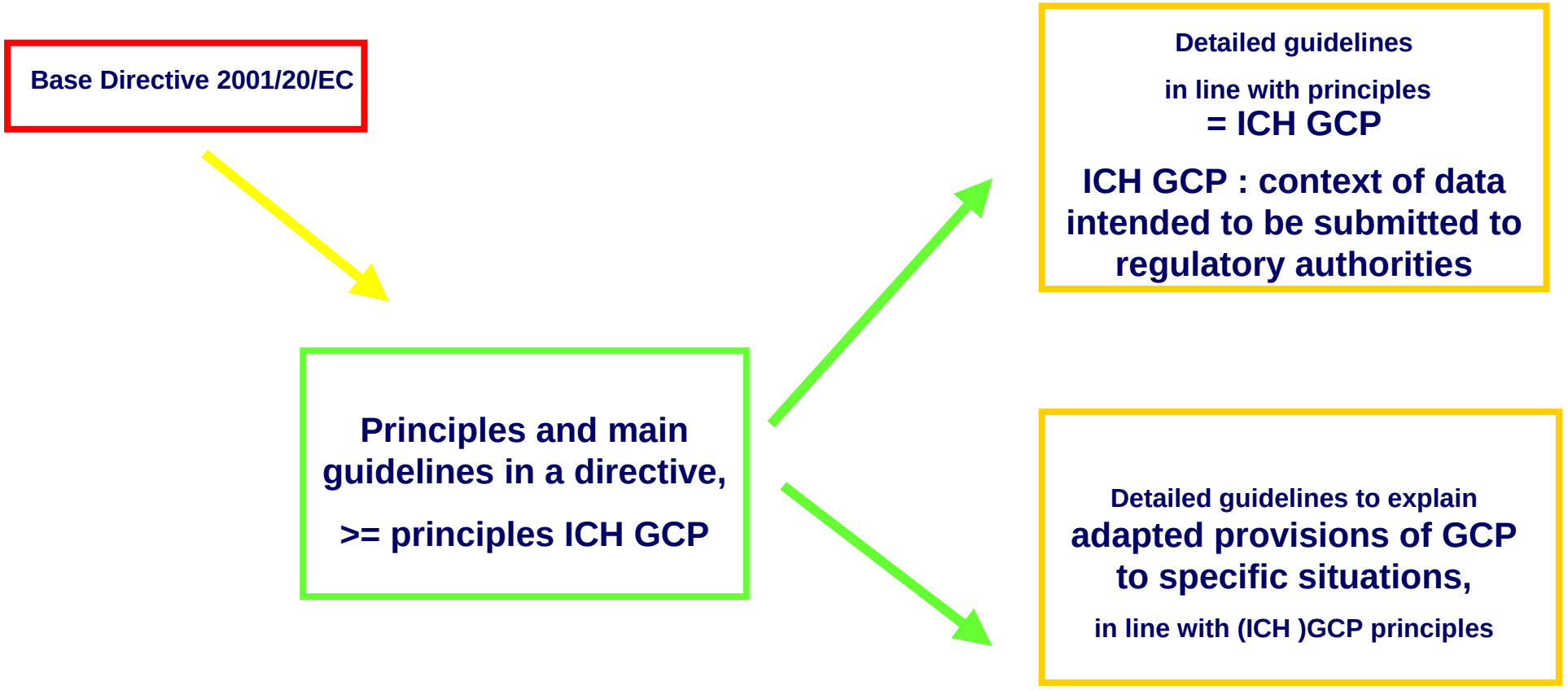
- ICH GCP referrred in the national law of some MS
- GCP principles and guidelines transposed in some MS
- Specific provisions for academic research in some MS (i.e. principles only)

**Need for a harmonised reference for GCPs as a EU standard**

# GCP inspections

## 1. Reference texts for GCP

### Suggestion : legal solution of a reference to (ICH) GCP




**See Article 47 Directive 2001/83/EC for GMP**

# GCP inspections

## Ethics Committees and GCPs

- Art. 6(1): Ethics committees shall adopt relevant rules of procedures (functions and operations) to implement the requirements set out in Dir 2001/20/EC Art. 6 and 7.

- Principles and guidelines for these rules of procedures are not detailed

- No full set of provisions in or referred to in the Directives that ensure that Ethics committees work in accordance with (ICH) GCP

# GCP inspections :legend

## Legal framework

**Legal framework**
**in place and adequate**

**Legal framework**
**not in place or inadequate**
**NOT CRITICAL**

**Legal framework**
**not in place or inadequate**
**CRITICAL**

## Guidance

**Guidance**
**in place and adequate**

**Guidance**
**to be developped**

**Directives: DIR20 = Directive 2001/20/EC**

**dir28 = Directive 2005/28/EC**

# GCP inspections
# 2. Implementation of National systems

- Trials under the scope of inspection


  * Trials conducted in EU
  * Trials submitted as part of application for MA (in EU or third countries)

- Principles of implementation of the system :


- Appointment of inspectors by Member States :


- Sites under the scope of inspection :

Ethics committee : to be listed in the definition of inspection
( Art 2(l) DIR )

# GCP inspections
## 3. Cooperation between MS and with EMEA

- Mutual recognition of inspection results

  Implies harmonization (see section 4)


- Request for assistance from one MS to another MS


- Request for inspections
  - By EMEA
  - New inspection in case of discordant views between MS
  - In third countries
  - From one MS to another MS (Art 27 dir)

# GCP inspections
## 3. Cooperation between MS and with EMEA

**- Communication / exchange of information**

1. Support

. Platform for inspectors (GCP-IWQ, EMEA)

**Implemented in 1997**

**2007 new mandate, objectives and rules of procedures**

. EudraCT

- Provision for inspection adequate


- Core set of mandatory data to be defined
- Harmonization of data entred by MS : policy to be implemented (« Data entry manual »)

# GCP inspections
## 3. Cooperation between MS and with EMEA

- **Communication / exchange of information**

**2. Operational issues:**

- Programs and plannings:
  - Visibility from inspectors:
    - procedures coordinated by EMEA: OK
    - links between some national programs:
      to be improved / information and cooperation

- Inspection outcomes:
  - Meta analysis of findings not easy
    => A common schema for categorization is in progress.

# GCP inspections
## 4. Quality and harmonisation of inspections

- Qualification and independence of inspectors


- Harmonization and training


  - **Procedures and guidelines on inspections:**

    * general recommendations : published in Vol 10

    * coordinated by EMEA : published procedures

    * core inspection guidance : draft to be adopted and published

- Training: Joint inspections, training services, sharing of experience

**ONGOING**

# GCP inspections
# 5. Inspection results

- Inspection reports


  - Avalaible to : *sponsor
    * other MS, EC , Agency, a request
    * other recipents, subject to arrangements (Community and MS)
    * Inspectee
    * MA applicant / holder

**Clarification/ Additional provisions needed**

- Transparency
  - Process to consult the GCP IWG not clear
  - Inspections findings and statistics /trends by categories :
    * to be publicly available – Management of confidential aspects
    * Requires harmonisation of thematic categorisation of findings

# THE CLINICAL TRIALS DIRECTIVE (Directive 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

**Pierre Henri BERTOYE (Afssaps, France)**
**on behalf of the**
**GCP Inspectors Working Group**

**Thank you**

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

**Prof. Dr iur Dominique Sprumont**
**EUREC/University of Neuchâtel**

**London, October 3, 2007**

# What aspects of the Directive 2001/20/EC and its implementing rules work well?

The Directive 2001/20/EC contributed to an overall improvement of the quality of CTs in European as well as to a better protection of human subjects

Member States had to formalize ethical review mechanisms and establish Ethics Committees and competent authorities

Researchers in non-commercial CT learned to work in compliance with the GCP requirements

The positive impact of the Directive is not limited to CT with medicinal products, but to biomedical research with human beings in general

# What does not work well?

The archiving of the documentation by the RECS for the minimum period of 3 years, according to the Directive 2005/28, is problematic at times due to a lack of resources and professional support

The definition of substantial amendment at article 10 of the Directive 2001/20 is not clear and gives too much room for various individual interpretation, resulting sometimes in either unnecessary or conversely inadequate information being provided to the RECs from the sponsors or competent authorities

Concerning safety information, RECs are frequently overloaded with information that is not relevant and does not add to their role of subject protection. Conversely it may sometimes limit their capacity to fulfil that role

# What does not work well?

RECs do not have systematic access to EU database (EudraCT, etc.). This may not be a general problem but from time to time it is crucial to be able to ascertain the status of a clinical trial and, at one point, it will be necessary to coordinate the system with international initiatives aiming at creating CT registries (i.e. ICTPR).

The stance on site specific assessments is unclear. RECs receive information about inspections only after they have been conducted even if they are central in the initial approval of CTs. At best they should take part in the inspections or at least be able to take position during the inspections

REC assessments, to the extend of their capacities, should be disregarded as they complement and enhance regulatory inspections as they consider the situation with a particular study in mind

# What can be remedied within the present legal framework?

- Article 3 should give guidance on means of waiver to informed consent in emergency situations where many member states have currently instituted individual rules
- Article 6 should make it an obligation on Member States to provide the necessary resources to the RECs in terms of finance, training, administrative support.
- Article 10 should be revised to make it an obligation for the sponsors to notify the RECs all amendments that are likely to have an impact on the safety of the subjects or to change the interpretation of the scientific documents in support of the conduct of the trial
- RECs should be granted the authority to temporary withhold a CT in case of non-compliance, the competent authorities being informed with the responsibility to review the situation within a short delay.

# What can be remedied within the present legal framework?

- Article 17 should be revised to define notification of SUSAR and other important safety information in a way that the RECs can properly evaluate the ratio benefits/risks without creating an adminstrative burden

- Article 15 should be revised in a way that RECs are informed of inspection and be given the opportunity to be involved in their conduct, at least to raise specific questions to be addressed during the inspection.

# What should a new legal framework look like?

- The revision should not be limited to the Directive 2001/20/EC but also cover other EU regulation of CTs, including CTs on medical devices and other types of research

- More attention should be given in this process to other existing sets of European regulation such as the Council of Europe Convention on Human Rights and Biomedicine and its additional protocol. A stronger coordination and consistency with those texts would be a great improvement for all stakeholders.

- We do not feel that the Directive should become a Regulation as cultural differences across Europe mean there will be diversity and not complete harmonisation. Yet standards should be high and universal.

# Thank you

# Bureaucratic obstacles to clinical trials: in the public interest?

Rory Collins
BHF Professor of Medicine & Epidemiology
Clinical Trial Service Unit
& Epidemiological Studies Unit
University of Oxford

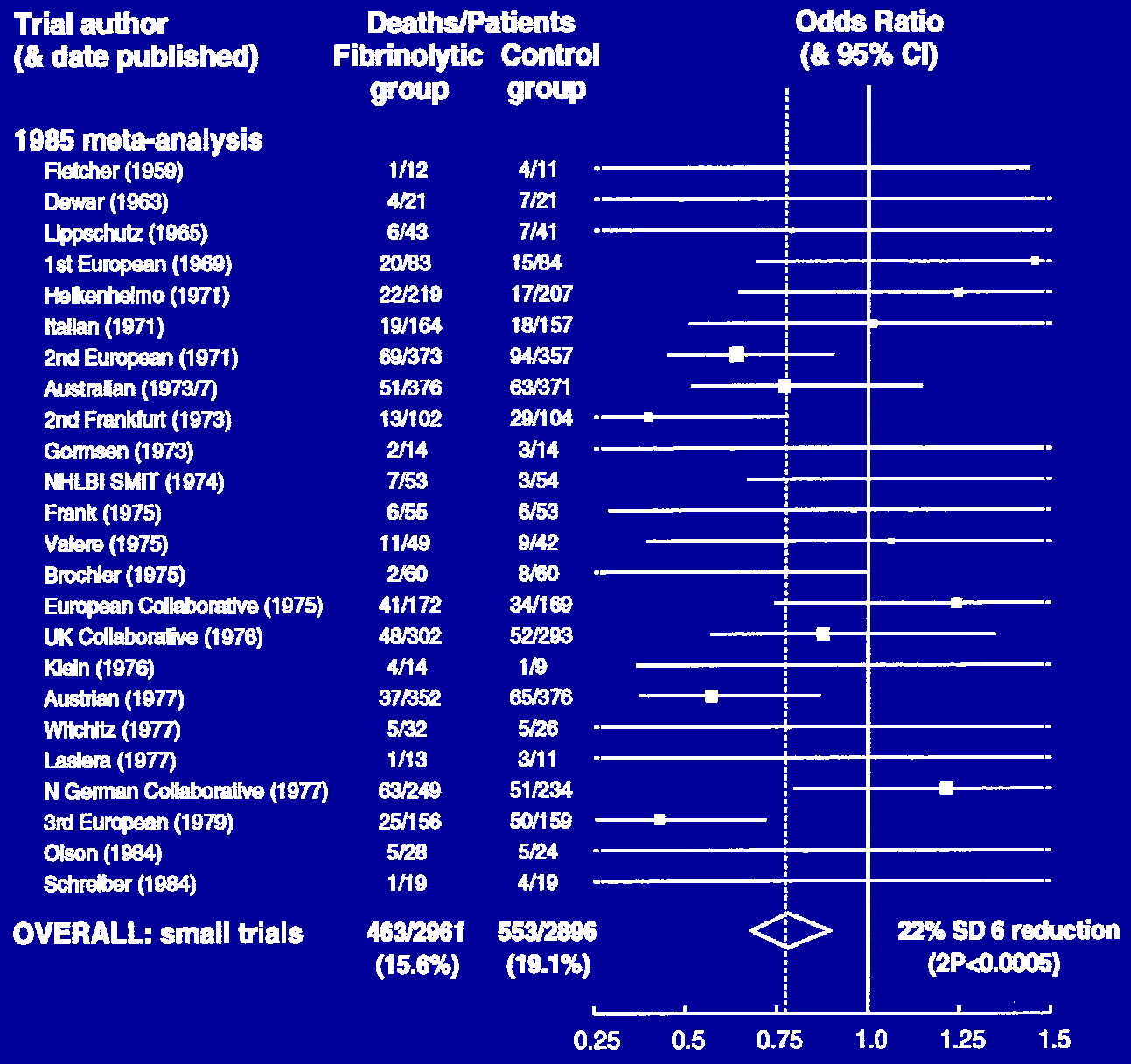
# Stated aim of the EU Directive on Clinical Trials

Article 1: *"This Directive establishes specific provisions regarding the conduct of clinical trials.... Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible."*

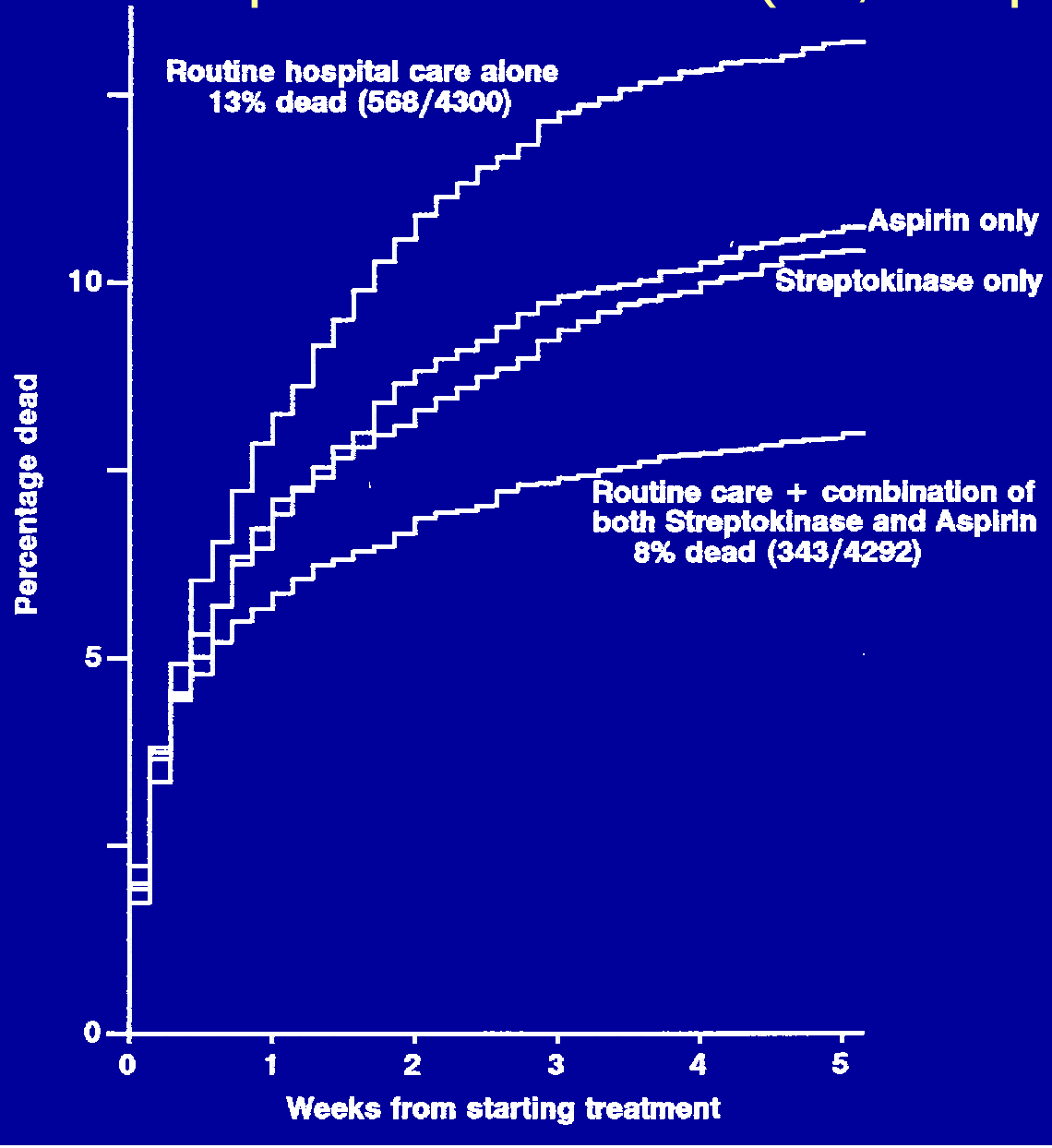
# Unanticipated consequences of good intentions

- MODERATE effects of treatments can have LARGE effects on public health
- RELIABLE assessment of MODERATE effects on mortality and major morbidity requires LARGE RANDOMISED trials
- Consequently, bureaucratic obstacles to LARGE RANDOMISED trials may well inadvertently REDUCE public safety

# Meta-analysis of small fibrinolytic trials (1959-85)



# ISIS-2: 2 x 2 “factorial” study of iv streptokinase and of oral aspirin in acute MI (17,000 patients)



# CR-UK assessment of impact of Clinical Trials Directive on UK non-commercial cancer trials (Eur J Cancer 2006)

- Doubling in costs of running non-commercial cancer trials and 6-12 month delays to starting
- Major concerns about correct interpretation due to lack of central guidance, lack of clarity regarding interpretation of guidance notes, and increased documentation
- Clinical trial units unable or unwilling to start in non-UK centres due to different interpretations in different European countries

# New EU Directive 2005/28/EC (Recital 11): streamlined procedures for non-commercial trials

*"Non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry may be of great benefit to the patients concerned…*
*…. The conditions under which the non-commercial research is conducted by public researchers, and the places where this research takes place, make the application of certain of the details of good clinical practice unnecessary or guaranteed by other means."*

# EU definition of “non-commercial clinical trials”

- ✓ Sponsor is a university, hospital, public scientific organisation, non-profit institution, patient organisation or researcher;
- ✓ Data from the trial should belong to non-commercial sponsor;
- ✓ Design, conduct, recording and reporting of the trial should be under control of non-commercial sponsor;
- x No agreement should be in place between this sponsor and third parties allowing them to use the data for regulatory or marketing purposes; and
- x The trial should not be part of the development programme for a marketing authorisation of a medicinal product.

N.B. Supplying a product free or at reduced cost or providing support in a limited way does not imply industry is “participating”.

# MRC/DH joint project on EU Directive identified site monitoring as a major cost

Proposed that approach to site visits may vary:

- Routine visits to all sites
- Visits to random selection of sites
- Target visits at less experienced sites and where central monitoring suggests problems

MRC/DH joint project (www.cl-toolkit.ac.uk)

# ICH GCP: Guidance on monitoring

*"… extent and nature of monitoring should be based on considerations such as the objectives, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring before, during and after the trial; however … central monitoring …can assure appropriate conduct of the trial in accordance with GCP"*

ICH GCP 5.18.3

# Report of International Society of Clinical Biostatistics subcommittee on misconduct in clinical trials (Statistics in Medicine 1999)

Misconduct is unlikely to affect study results if any of the following conditions hold:

- The misconduct is limited to a few investigators (eg, one centre in a multicentre setting) and/or to a few data items;
- The misconduct bears on secondary variables that have little or no effect on the primary endpoint of the study; or
- The misconduct affects all treatment groups equally, and hence does not bias the results of the study.

NB: Misconduct committed without regard to the treatment assignments (for example, prior to randomization or in Double-blind trials) generates noise but no bias.

*"….. fraud in clinical trials is so rare and …. generally inconsequential, that the public may be far more misguided by studies that are poorly designed, wrongly analysed and inappropriately reported than by fraud"*

ISCB subcommittee
Stat Med 1999

*“The growing number of regulations ….. may also have the unintended consequence of making trials ever more complex ….. such complexity may be counterproductive and may pave the way to fraud”*

ISCB subcommittee
Stat Med 1999

Proliferation of laws and guidelines may make clinical research LESS reliable

(and so HARM, not help, patients)

Thank you

# CLINICAL TRIALS DIRECTIVE

MARIO NEGRI
ISTITUTO DI RICERCHE FARMACOLOGICHE

SILVIO GARATTINI

**London 3rd October 2007**

# WHAT ASPECTS OF THE DIRECTIVE 2001/20/EC AND ITS IMPLEMENTING RULES WORK WELL ?

- A PROCESS OF HARMONIZATION FOR THE 27 MEMBER STATES
- AN HELP TO ACADEMIC CLINICAL INVESTIGATORS FOR THE IMPROVEMENT OF
  - DATA COLLECTION
  - MONITORING
  - ARCHIVES
- A STIMULUS TO INCREASE UTILIZATION OF ELECTRONIC AND INFORMATICS TECHNOLOGY

# WHAT DOES NOT WORK WELL?

- RED TAPE AND BUREAUCRATIC REQUIREMENTS HAVE INCREASED
- COST OF TRIALS HAS INCREASED 2-4 TIMES
- APPROVAL OF MULTICENTER INTERNATIONAL TRIALS IS MORE COMPLICATED
- NUMBER OF INDEPENDENT TRIALS HAS DROPPED

# WHAT CAN BE REMEDIED WITHIN THE PRESENT LEGAL FRAMEWORK?

- DEFINITION OF INDEPENDENT (ACADEMIC/NON-PROFIT) TRIALS
- RECOGNITION OF THEIR IMPORTANCE FOR THE CURRENT EVALUATION OF MEDICINAL PRODUCTS
- HARMONISATION OF PROVISIONS IN FAVOUR OF INDEPENDENT TRIALS (WAIVER OF FEES, INSURANCE AND COST OF DRUGS)
- ACCESS TO THE EUROPEAN DATABASE OF CLINICAL TRIALS
- CLASSIFICATION OF THE REQUIREMENT FOR GCP IN RELATION TO THE RISK OF THE PRODUCT FOR PATIENTS.

# APPLICATION OF GCP IN RELATION TO RISK OF PATIENTS

(i) COMPOUNDS BEING INVESTIGATED TO OBTAIN MARKETING APPROVAL

(ii) COMPOUNDS BEING INVESTIGATED WITH “ORPHAN DESIGNATION”

(iii) MEDICINAL PRODUCTS ALREADY ON THE MARKET

(iv) MEDICINAL PRODUCTS CONFIRMED AFTER 5 YEARS OF UTILIZATION

(v) MEDICINAL PRODUCTS UTILIZED FOR “MINIMAL INTERVENTIONS”

# WHAT SHOULD A NEW LEGAL FRAMEWORK LOOK LIKE?

- SWITCH THE REFERENCE DG FROM ENTERPRISE TO SANCO-RESEARCH
- INTRODUCE THE CONCEPT OF “ADDED VALUE” FOR NEW MEDICINAL PRODUCT
- ONE OF THE PHASE III TRIALS SHOULD BE DONE BY AN INDEPENDENT ORGANIZATION
- EXTEND GCP LEGISLATION TO ALL CLINICAL TRIALS FOR DIAGNOSTICS, MEDICINAL DEVICES, HERBAL AND HOMEOPATHIC REMEDIES
- ABOLISH CONFIDENTIALITY OF PHARMACOLOGICAL AND CLINICAL DATA UTILIZED FOR DRUG APPROVAL
- DEVISE A MINIMAL SET OF RULES TO BE APPLIED BY ALL ETHICS COMMITTEES (PLACEBO, EQUIVALENCE, INFORMED CONSENT, SURROGATE END-POINTS). NEED OF A WORKSHOP.

**Thank you**

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

*Session 4 – Potential solutions and recommendations for the future*

*Jacques Demotes-Mainard, INSERM*
ECRIN

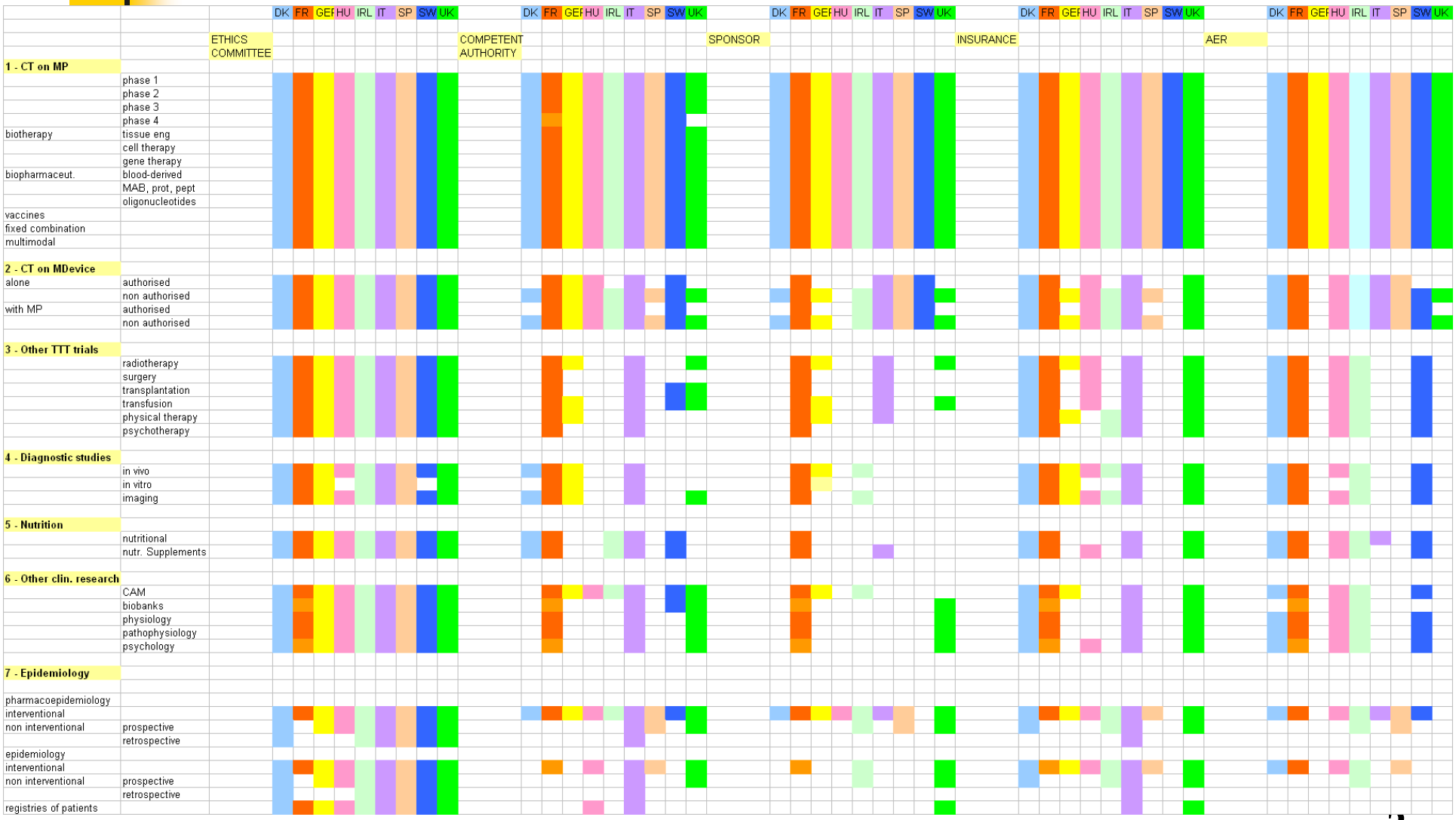
**Please note that these presentation slides will be included in appendix to the report of the meeting and published at the same time.**

# What aspects of the Directive 2001/20/EC and its implementing rules work well?

- partial harmonisation in the conduct of clinical trials on medicinal products
- integration of clinical trials identification and adverse event reporting (EudraCT, EudraVigilance)
- single opinion from ethics committees, responsibility of the sponsor and of the state (through the competent authority)
- increase in quality and GCP compliance, fosters the development of the clinical research infrastructure

# Comparison of national requirements

EC CA sponsor insurance AER



# What does not work well?

- Harmonisation / integration
  - integration whenever possible
  - if not possible guidance, coordination, accreditation
- Directive / regulation / guidance
  - negative aspects of divergent interpretation of the Directive
- Field of the Directive
  - Legislation covering clinical research other than clinical trials on medicinal product, prepared by DG SANCO, DG Research, DG Enterprises and Industry

  - with health products (competent authority)
  - without health product
  - interventional or observational

# What does not work well?

- Competent authority : integration
  - at least in multinational trials: centralized ? mutual recognition ?
- Ethics committees : accreditation
  - harmonisation, training, quality assurance, methodological assessment
- Multiple sponsors
  - sharing roles and responsibilities on a contractual basis
- Categories of research
  - interventional vs. non-interventional
  - intermediate category ?
  - psychological assessment
  - medicinal products vs. nutritional supplements
  - definition of categories of research based on the risk

# What does not work well?

- Definition of non-commercial trials ?
  - replaced by risk-based adaptations (monitoring etc...)
    -> hazard to participants, to study, to public health
- Support measures for academic institutions
  - use of data for registration purposes
  - waiver / fees to competent authorities
  - waiver of purchasing IMP
  - insurance covered by public health system
  - support to SUSAR reporting
  - IMP dossier, labelling
  - development of the infrastructure, funding

# What can be remedied within the present legal framework?

- Guidance on interaction between EC and CA (one-stop shop ?)
- SUSAR reporting to EC
- Information on national requirement, helpdesk
- Unambiguous IMP definition
- Unambiguous definition of substantial amendments
- Uniform GMP requirements for biotherapy
- Training of investigators, nurses and specialised staff
- Harmonised and appropriate methodological assessment by ethics committees and competent authorities

Thank you

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

John Poland, ACRO

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

**Please note that these presentation slides will be included in appendix to the report of the meeting and published at the same time.**

# Association of Clinical Research Organizations

- ACRO member companies:
  - Full-service CROs conducting clinical trials in over 60 countries worldwide
  - 120 EEA offices with over 11,000 staff involved in clinical trials throughout the EEA
  - In 2004, managed over 22,000 Phase I-IV studies at more than 152,000 investigative sites globally
  - Broad perspective across clinical trial stakeholders



ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

# What aspects of the Directive 2001/20/EC and its implementing rules work well?

- Acceptance of common IMP Dossier by most competent authorities
- Acceptance of common (EudraCT) application form by most competent authorities
- Predictable timelines for review of applications and substantial amendments by competent authorities and ethics committees in most member states
- Legal basis for Good Clinical Practice (GCP)
- Sharing of information between competent authorities (EudraCT) promotes the safety of research participants



ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

# What does not work well?

- Disharmony in documentation requirements for submission to competent authorities and ethics committees
- Disharmony in procedures for competent authority and ethics committee review
- Legal representative requirement
- Confusion around the concept of a single sponsor for a trial
- Amendments arrangements
- SUSAR reporting requirements

# What does not work well? (continued)

- Disharmony/lack of transparency in GCP standards
- Coordination of GCP inspections
- Disharmony in definition of an IMP
- Disharmony in importation requirements for IMPs
- National laws ambiguous or duplicate EEA-level requirements
- Factors not regulated by Directive 2001/20/EC, e.g. investigator/institution contracts

# What can be remedied within the present legal framework?

- Improved communication mechanisms on GCP standards
- Greater coordination of GCP inspections (principle of no more than one routine inspection per trial for the EEA)
- Mechanism for CROs to register once only with EudraVigilance
  - CRO (unless acting as sponsor, applicant or marketing authorization holder) cannot become a registered organization within the EudraVigilance Community
  - But why not allow cross-reference to data already submitted?
- Training of ethics committees in clinical trials law

# What can be remedied with changes to guidelines?

- Unambiguous and unified standard for:
  - Format and content of clinical trial applications to competent authorities and ethics committees
  - What requires submission as a substantial amendment
  - Format and content of Annual Safety Report, based on a single report for all trials in a clinical development programme
  - Definition of an IMP and the data to be submitted for different types of IMP



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# What should a new legal framework look like?

- Ideal – single competent authority and single ethics committee approval for a multinational trial across EEA
- “Second best” – pan-EEA office to monitor and provide rapid resolution on issues of implementation and disharmony
- Unified standards for application and substantial amendments to all competent authorities and ethics committees
- True centralized ethics committee review
- Enforce legal timelines for review



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# What should a new legal framework look like?

- Authorized representative instead of legal representative, with civil and criminal liability retained by sponsor
- Unified standards for all aspects of SUSAR reporting
- Expedited process for implementation of “efficacy” amendments (i.e., to permit rapid closure of a trial arm that is not proving effective)
- No separate importation approval after competent authority approval
- Standard template for sponsor agreements with investigators and institutions



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Thank you

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

**Dagmar Chase, EUCROF**

EU CRO Federation

**Please note that these presentation slides will be included in appendix to the report of the meeting and published at the same time.**

# What aspects of the Directive 2001/20/EC and its implementing rules work well?

- Single CTA form for all Member States (MS)
- Reduced timelines
  - CA authorisation
  - EC opinion – where adhered to
- Single EC opinion per MS – where implemented correctly
- IMP batch release by qualified person (QP) (no inspection of GMP site required)

# What does not work well?

- CA and EC submission of required documents ("list behind the list")
- Sometimes very regional CA procedures (eg., Italy)
- Large diversity as to EC procedures in general
  - Application forms (within MS and across MS)
  - Implementation of single opinion not adhered to (eg., Italy)
  - Timelines (eg., in Spain submission on certain days only)
- Handling of substantial amendments
  - Disharmony as to assessment of substantial / non substantial
  - Disharmony as to handling of non substantial amendments

# What does not work well?

- Import licence still needed in some MS after batch release in the EU
- Labelling not according to Annex 13 (eg., Germany)

# What does not work well?

- Large diversity as to SUSAR reporting ➔ over reporting
  - Reporting procedures for marketed IMPs not clear
  - Disharmony as to periodic line listings
  - Confusion as to blinded/unblinded reporting to investigators
- Eudravigilance
  - Sponsor has to sign that all studies are covered by the same legal representative
  - Extremely complex and difficult to handle for CROs and non-commercial sponsors

# What does not work well?

Confusion around the concept of legal representative

- 2001/20/EC Article 19
  „This Directive is without prejudice to the **civil and criminal liability of the sponsor** or the investigator. To this end, the **sponsor or a legal representative** of the sponsor must be established in the Community"

- Questions and Answers: Clinical Trial Documents, April 2006, states under Question 3a that the **legal representative shall be responsible for the civil and criminal liability** of the sponsor in respect of the clinical trial.

# What does not work well?

Confusion around the concept of legal representative

**MHRA website, FAQ: The legal representative**

- .....
- should be willing to act as the **agent** of the sponsor in the event of any legal proceedings instituted in the EEA (for example, for service of legal documents)
- should be established and **contactable at an address in the EEA**
- **does not assume any of the legal liabilities of the sponsor(s) for the trial by virtue of the role of legal representative and does not therefore require insurance or indemnity to meet such liabilities**, but may in some cases enter into specific contractual arrangements to undertake some or all of the statutory duties of the sponsor in relation to the trial, in which case the legal representative would also be regarded as a co-sponsor and would then require insurance or indemnity cover.

# What does not work well?

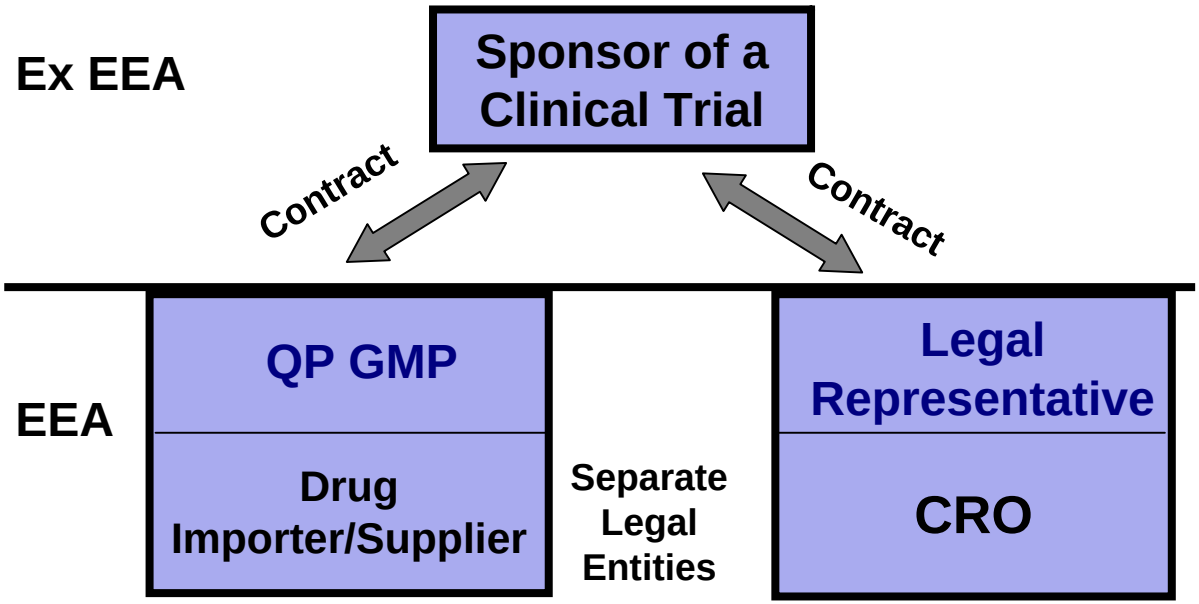
## Confusion around the concept of legal representative

**Different CROs - different approaches**

- CROs take on the role of LP **not** knowing what the implications might be
- CROs found a separate company (legal entity) only offering the LP service, hoping that in case of damage the mother company will not be negatively (financially) affected
- CROs are advised by lawyers not to take on the LP role
  - rely on somebody else, eg., somebody in the UK
  - help build a sponsor affiliate which is an empty shell with the managing director located in the country of the sponsor (i.e. not in the EU/EEA)

# What does not work well?

Confusion around the concept of legal representative




- Who is liable in the scenario illustrated above in case of quality issues with the IMP?
- Relationship between QP and Legal Representative not clear

# What can be remedied within the present legal framework?

- Stricter controls of correct implementation of Directive 2001/20/EC by EU Commission, especially with respect to implementation of EC procedures

# What should a new legal framework look like?

- "Legal Representative" ➔ "Agent" without liability
- New legal framework to guarantee harmonisation of procedures
  - Detailed guidance documents ➔ Directive
  - Regulation?
- A central approach would be very much favoured by EUCROF for multi-national trials
  - Review of initial application by two MS (CAs and central ECs)
  - Review of amendments by the same two MS (CAs/ECs)
  - Involvement of local ECs strictly limited to assessment of suitability of sites (no acceptance/rejection of protocol)

Thank you

EMEA Scientific Committees Working Party with Patients' and Consumers' Organisations

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

**Mr. Nikos Dedes**
**Co-Chair**
**Patients' and Consumers' Organisations Working Party - EMEA**

# EU Directive

- The EU Directive wanted to provide a clearly defined legal mandate to sponsors, investigators, regulators and Ethics committees on GCP

- Simplify and harmonize administrative procedures and speed up clinical research

# Good Clinical Practice

- "…set of internationally recognized ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials…"

- "Compliance with GCP provides assurance that the rights, safety and well being of trial participants are protected and that the results of the clinical trials are credible"

# Themes

- Participants / Patients
  - Rights (Autonomy)
  - Informed Consent
  - Protection of personal data
  - Safety
  - Special protection of incapable to consent
- Transparency
  - Innovation
  - Improved scientific quality
  - Avoidance of unnecessary repetition
    Registries, Publication of results
  - Information between NCA & Ethics Committees
- Expediency
  - Harmonisation of requirements between NCAs
  - Harmonisation between Ethics Committees
  - Single opinion

# Aspects of the directive that work well

A. The Directive has provided for more transparent procedures and greater level of protection of individuals
B. It has promoted a more rational conduct of clinical trials
C. It has improved patients' rights protection both in industry funded and in investigators driven trials
D. Despite the increased administrative burden it has improved the level of consistency in the conduct of independent investigators driven trials

# What aspects of the directive do not work well?

A. Lack of availability of information on ongoing/concluded clinical trials to the patients and general public (Article11)
B. Non-interventional clinical trials are not covered by the current legal text
C. Lack of European ethical common dimension is acknowledged
D. Heterogeneity in Ethics Committees:
    A. -composition differs amongst different MS,
    B. -Lack of coordination in their conclusions across different MS
E. Protection of clinical trial subjects (Article 3). Significant differences of "Informed consents" across Europe both in term of quality and quantity of the information provided

# What can be remedied within the present legal framework?

A. Need for more patient and patient-specific involvement as part of Ethics Committees

B. Need for "informed consent" guidelines aiming for harmonised approach across EU both in terms of content and structure :

   -readability testing?

   -Particular consideration for current heterogeneity of "informed consent" for people unable to give consent/legal representative

C. Need for consistent and continuous provision of information to patients during and after finalisation of the clinical trial

D. Need to offer extent of treatment at the end of the trial free of charge for patients

# What should a new legal framework look like?

1. Legislation should give provision to make information on trials entered in EudraCT accessible to public

2. Results must be made available within defined timeline (e.g. one year from completion)

3. Legislation should provide for a minimum delay in time from Ethics Committees when they give an opinion, in order to ensure that a proper evaluation is performed

4. Legislation to cover non-interventional clinical trials in order to consistently regulate all clinical trials in EU

# Thank you

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

Potential solutions and recommendations for the future

Alan Morrison, Vice-President International Regulatory and Safety, Amgen

- The Directive and Member State implementing legislation should be reviewed
- Essential for the competitiveness of the EU as a centre for:
  - Innovation
  - Clinical research

## Amending the Directive to ensure:

- Clear provisions and definitions
- Streamlined review processes
  - Roles and responsibilities of ECs and NCAs identified
  - Mutual recognition of NCA assessments
  - Enhanced role of the CTFG
- Single point of entry for submission of CTA applications and harmonised data requirements for all Member States
- Centralised safety reporting

**Thank you**

European Federation of Pharmaceutical Industries and Associations

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

# Session 4: « Potential solutions and Recommendations for the Future »

**Mats Ericson, Ph.D**

/Wyeth Research/

**on behalf of EFPIA**

# Recommendations for the Future

- There may be no benefit in a drastic overhaul of the CT Directive
  - But, improvements to clinical trial authorisations MUST be sought at different levels
- **Level 1:** Renew stakeholder commitment to the Directive implementation harmonisation effort:
  - (e.g., remove national exceptions from EU guidelines, adhere to agreed EU guidelines, refrain from issuing national guidelines)
- **Level 2:** Amend Directive to address certain issues:
  - (public health interest, e.g.,safety reporting)



efpia

# Recommendations for the Future (cont.)

- **Level 3:** Create a new <u>additional</u> alternative procedure
  - Current duplicate assessments are not best use of EU resources. This is a fundamental flaw in the Directive which cannot be addressed within the current framework
  - A new optional procedure with one assessment, a single approval per study would be particularly suitable for multinational studies
  - *Key issues to address: body responsible for scientific review? resources and budget? how to transpose « approvals » to all concerned member states? could procedure be extended to include a single EC review?*



efpia

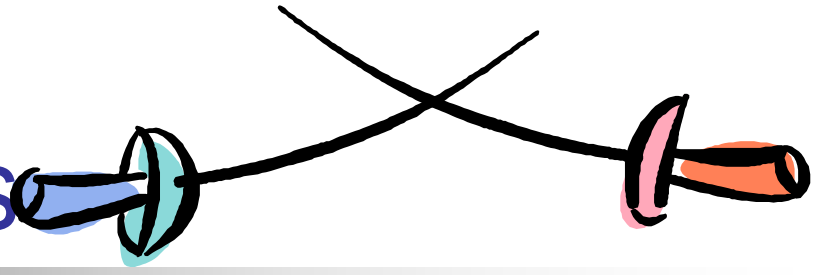
Thank you

# Potential solutions and recommendations for the future

From the point of view of ethics committees

Ms Ritva Halila – EUREC/NCA Finland

# Law and ethics



- two-headed sword
- Directive 2001/20/EU has a good purpose; includes a lot of details that can be followed in most of the situations
- because of detailed text excludes a patient group most vulnerable and in most critical condition from benefits of medicinal research

# Directive 2001/20/EC

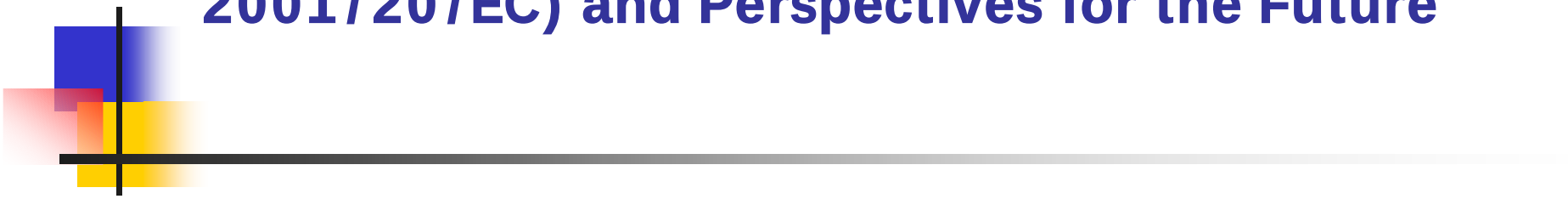
- clinical trials in emergency situations
- - > Amendment in the directive
  - ETS 195 Article 19
  - Exceptions to conduct research with written informed consent: consent cannot be obtained
    - Urgency
    - Patient´s state of health
    - Expected to be of immediate benefit to the patient´s health
    - Consent will be sought as soon as medically possible from the RP or his family members

# More synergy, less duplicate work

- more clear separation of duties of competent authority and EC:s
  - change of the directive
  - -> more efficient work of EC and CA
- Education of EC:s
  - obligation of the member states to provide
  - amendment in the directive
- SUSARs
  - change of the directive

# Thank you

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



**Session 4**

**Chantal Bélorgey,**
**CTFG (Afssaps/France)**

# Issues

- **Objectives of the directive** :
  - **Protection of subjects**
  - **Good practices**
  - **Harmonised technical requirements to conduct and follow up CTs**
  - **Exchange of information**
- ***Broadly achieved***

- **Scope of improvement**
- ***Regulatory and scientific cohesion across MS :***
  - **Processes :**
    - **CTA content and assessment**
    - **Amendments**
    - **SUSARs notification and assessment**
  - **Transparency**
  - **Safety of CTs (FIH-CTs)**

# How to improve ?

## 1. Harmonisation :

- ***Reinforcement of collaboration by MS :***
  - Harmonisation by CTFG :
    - Scientific assessment sharing of multinational CTs
    - What is a substantial amendement ?
  - Pharmacovigilance work sharing by NCAs (new legal framework)
  - Definition of conditions for research sites/FIH CTs

## 2. Simplification / clarification :

- Clarify SUSARs and SARs reporting-assessment
- Simplify ECs information on SUSARs
- Mandate electronic reporting of Susars (new legal framework)
- Train (academic) sponsors (Eudravigilance, MedDRA...)
- Refer to ICH GCP

## 3. Prerequites: **improve data sharing beetween MS via information systems**

## 4. Transparency

- Information exchange with stakeholders (CTFG)
- An European CT public register (new legal framework)
- Availability on line of recommendations, Q and A...

- **CTs : an essential role in bringing innovative medicines as quickly as possible to patients**

- **Cohesion, simplification and transparency : keys for the success of the European research**

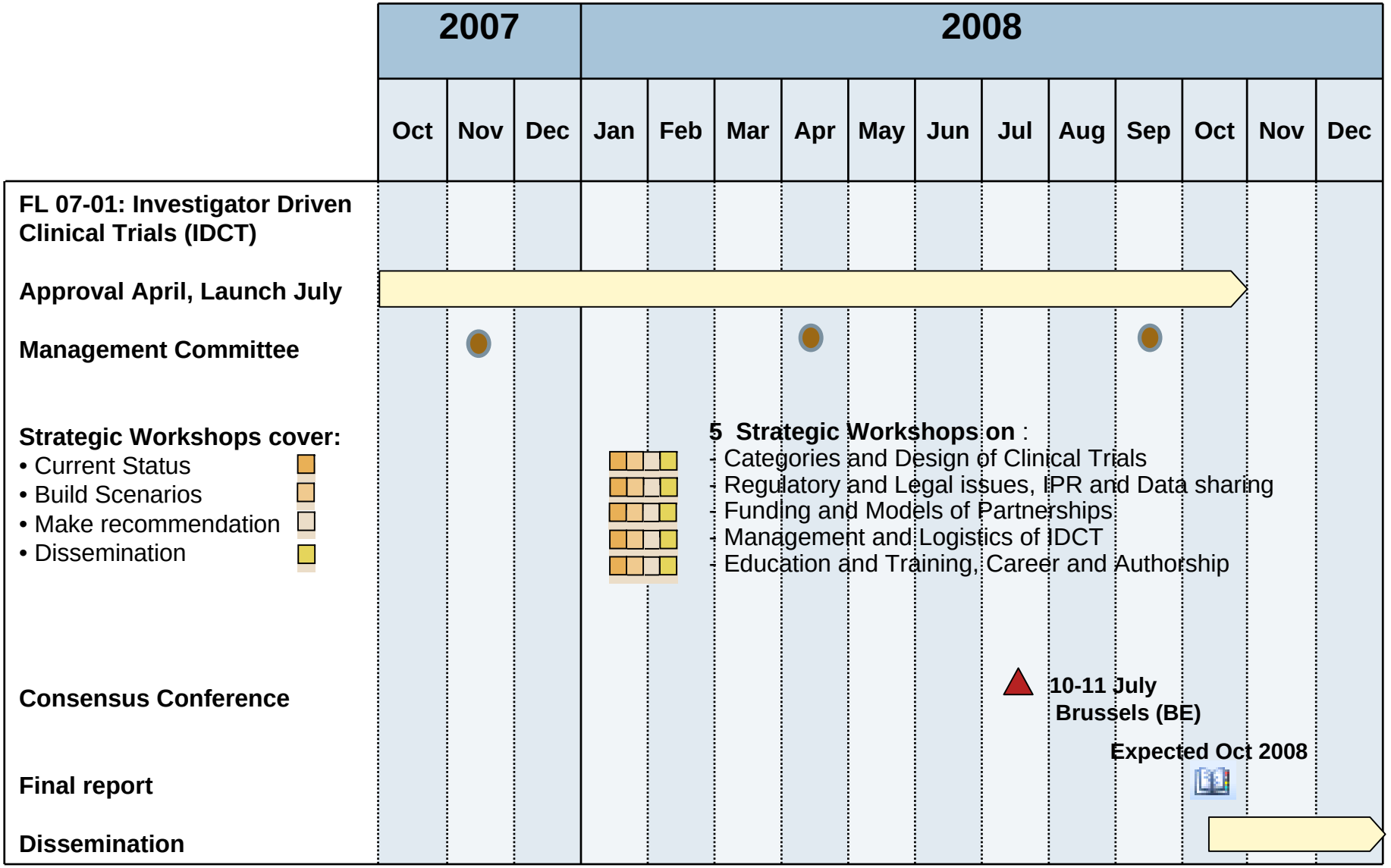
**Thank you**

EUROPEAN SCIENCE FOUNDATION
SETTING SCIENCE AGENDAS FOR EUROPE

# Session 5

**Stefan Bielack**
**ESF/EMRC**
**Olgahospital Stuttgart, Germany**

# FL 07-01 Investigator Driven Clinical Trials Workplan



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# Thank you

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

*Session 5 - General discussion*

*Jacques Demotes-Mainard, INSERM*

ECRIN

# What should a new legal framework look like?

- A single and comprehensive legislation covering all clinical research
- protecting the participants according to the risk associated to the category of study, not to its commercial or non-commercial objective
- with a single assessment by one competent authority
- with accredited ethics committees
- with a clear guidance on their respective roles and harmonised interactions
- promoting trust, transparency and optimal use of data through open registration, reporting, and data repositories

*Thank you*

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

[ Final stakeholders views ]

**François R. CHAPUIS**

**on behalf of the**

**E U R E C network**

***European Network of Research Ethics Committees***

**London, 3rd October 2007**

# Expectations EC/EMEA meeting

- “The meeting represents a unique opportunity to set out what works well, issues that give rise to problems and recommendations for the future.”

- “Speakers and panellists should ensure they make full use of this opportunity.”

# What aspects of the Directive 2001/20/EC and its implementing rules **work well? [ 1 ]**

- Research on human subjects
  = Intervention + Person

- Directive 2001/ 20 / EC
  = Drug + Person

| *Competent Authority* (Protect drug) | | *REC Ethics Committee* (Protect people) |
|---|---|---|

Advance in harmonisation in Europe +++

# What aspects of the Directive 2001/20/EC and its implementing rules **work well? [ 2 ]**

- 60 days maximum
  are respected (around 35 days mostly)
  (see JAMA paper 2006)
- Public trust in Authorisations or Favourable Advices delivered by Ethics Committees +++
- Clinical research is conducted and published in a safe and confident way in Europe

# What **does not work well?**

- SUSAR:
  - too much information
  - no synthesis
- Financial Independence of Committees?
- Drug and Non-Drug research evaluation
- Specific situations (minor adaptation needed)
  - Paediatrics
  - Clinical research in emergency situations...

# What can be remedied within the **present legal framework? [ 1 ]**

- SUSAR: synthetic report is needed:
  - DSMB ? and/or sponsor ?
  - validation by Competent Authority
  - information to Ethics Committees
- Access to EudraCT & EudraVigilance
- Networking between the European Countries
  - for industry... for NCA...
  - for patients...
  - for investigators...
  - for sponsors... commercial and non-
  - for Research Ethics Committees... EUREC

## What can be remedied within the **present legal framework? [ 2 ]**

e.g., EUREC initiative for Ethics Committees:

- Training and education: case-studies database
- Criteria for validation of training programmes and training curricula
- Development of harmonised documents
- RECs quality management and self-evaluation
- Communication between ethics committees
- Focus on new member states...

# What should a new **legal framework** look like?

- Minor changes to the current Directive
- No European centralisation of Ethics
  (= respect each country's culture)
  and no regulation
- Involvement of lay persons
- Methodology evaluated by RECs
  "if not scientific, therefore not ethical"
- Independence of Committees guaranteed

- In case of a revision... should be Minor...
- Goal = **development** (No decrease)
  - in protection of human subjects,
  - in all types of clinical research

- Protection $\Leftrightarrow$ Protection

  **drug** $< \neq >$ **human subjects**

# Thank you

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

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# What aspects of the Directive 2001/20/EC and its implementing rules work well?

- Legislative harmonisation (same rules in EU member states).
- Integration of trials' identification and adverse events' reporting (EudraCT, EudraVigilance)
- Clear identification of the role of Sponsors, Competent Authorirties and Ethical Committees within the conduct of a clinical trial

# What aspects of the Directive 2001/20/EC and its implementing rules work well?

- Dissemination and Implementation of the Good Clinical Practice rules
- Exploitment of the level of quality of management of private and public institutions (sponsor duties)
- Increased investment in clinical research

# What can be improved?

- **Harmonisation (transposition)**
  - excessive admnistrative burden
  - complex responsibility management (e.g.single sponsorhip)

**Decrease in number of « non commercial trials »**

[Hoey R, The Lancet, 369, 1777]

**Increase of costs**

[Heran J, Sullivan , Eur J Cancer 2007, 43, 8; Hoey R, The Lancet, 369, 1777]

# What can be improved?

- **Definition of “non commercial clinical trial”**

***- EC-RTD-F specificities***

* in the funding activities in « non commercial clinical trials » run with Academia only in the interest of the Patients;

* in the funding activities whereas SMEs are involved in research projects.

- Potential equivalence of data obtained in « non commercial clinical trials » with regards to marketing authorisation;

***- SME specificities***

* pivotal role in the development of new innovative therapies;

* sponsorship

*Thank you*