REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC
CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION
France position

France welcomes the Commission's proposals with the view to protect the clinical trials'subjects, to ensure clinical (CT) data reliability and to simplify the EU clinical trials system. We support also the general goal consisting in facilitating CTs in Europe by harmonisation of the requirements and processes, coordinating assessments of the CT applications (CTA) by the MS and in deciding finally at the national level.

1. COOPERATION IN ASSESSING AND FOLLOWING UP APPLICATIONS FOR CLINICAL TRIALS

1.1. Single submission with separate assessment

Commission's preliminary appraisal: A single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned.

Consultation item no. 1: Do you agree with this appraisal? Please comment.

France strongly supports the principle of a single submission of CTA, namely an electronic submission to all MS concerned (MSC) through a single EU portal, including applications to NCAs and to Ethics Committees (EC). The feasibility of such a system requires nevertheless further investigations with the participation of the member states (MS).

Commission's preliminary appraisal: a separate assessment would insufficiently address the issue set out above: the difficulties created by independent assessments would remain.

Consultation item no. 2: Do you agree with this appraisal? Please comment.

France agrees that the current system is not the more appropriate for the multinational clinical trials (around 25% of CTs performed in EU), in terms of efficiency and harmonization.

1.2. Single submission with subsequent central assessment

Commission's preliminary appraisal: a central assessment is not appropriate for clinical trials approval and would, as regards clinical trials, not be workable in practice for the following reasons:

- this option would insufficiently take account of ethical, national, and local perspectives. For these aspects, a parallel, national, procedure would have to be established in any case.
- the sheer number of multinational clinical trial per year (approx. 1200) would make centralised assessment very difficult. To this would add all substantial amendments of the clinical trials.
- the involvement of all member state is not needed, as very few clinical trials are rolled out in more than five or six member states.
  Moreover, a Committee structure requires frequent meetings with a robust supporting infrastructure. The costs (and, consequently, fees) involved would make this mechanism unattractive for academic researches.

Consultation item no. 3: Do you agree with this appraisal? Please comment.

France agrees that a central process similar to the MA Centralised Procedure would not be the more convenient as it is too heavy, not enough flexible, not appropriate to the high number of applications, not taking into account local aspects of CTs and involving a Committee with all MS although they should not be all concerned by the trial (only 10% of the EU CTs concern more than 4 MS).

1.3. Single submission with a subsequent 'coordinated assessment procedure' (CAP)

The CAP process, as it is proposed by the Commission, involves several new principles:
- Maintaining national decisions for CTAs and authorisations of substantial amendments
- Input of concerned MS in the assessment of CTs with a reporting MS (RMS) to lead the assessment of multinational CTA,
- EMA's role as the secretariat of CAP
- A joint assessment by the MS concerned (MSC) on predefined issues and a national assessment for ethical and local aspects of the CT.
- A single national approval of the CT as a whole, including national competent authorities (NCA) and Ethics Committee (EC) assessment and including aspects related to the limited joint assessment and the ethical/local aspects of CTA
- Definition of the scope of what should be assessed in cooperation by the MS concerned (joint assessment/section a) and what should be assessed nationally (ethical and local aspects/sections b and c)
- Involvement of both NCAs and ECs in the process, without defining at a Community level exactly the scope of each body (letting each MS organise the distribution of tasks).
- 60-Day period for the 'single whole' national decision.

Commission's preliminary appraisal: The CAP could offer a sufficiently flexible approach. It allows for a joint assessment without a cumbersome committee structure. It would allow national practice to be taken into account. It would respect that, as a basic rule, ethical issues clearly fall within the ambit of Member States.

France strongly supports the general principle of a coordinated assessment by the MS concerned, as well as the principle of keeping the CT approval at the national level maintaining the MS responsibilities on CTs conducted in their territories.

The principle of a coordinated assessment with a RMS coordinating all the MSC assessment and building up one common decision is supported, as it is currently set up in the voluntary harmonisation procedure (VHP) which has been set up by the Clinical Trials Facilitation Group (CTFG) of the Heads of Medicines Agencies (HMA). In that context, we think that the CAP should benefit from the VHP experience. It is important to notice for instance that one of the most tricky difficulty in the VHP is the single decision (NCA + EC) laid down by national laws in some MS, which significantly increased the process timelines.

Taking into account the experience of the CTFG, we think that this network of NCAs in charge of assessing CTs in EU should be recognised as the co-ordinator of the CAP. We think that the secretariat of CAP should be ensured more efficiently by the HMA CTFG itself, EMA being responsible for maintaining the current CT databases (EudraCT and EVCTM).

The single national decision resulting of the 2 assessments by NCAs and Ethics Committees (ECs), might be difficult to achieve within 60 days; also it may be appropriate to keep the general principles of independence of NCA and EC procedures.
Furthermore, this system would conduct ECs to reorganise their own process in order to be able to give a final opinion within 60 days, meaning they will not get anymore the possibility to use a clock stop, nor the sequential approach. Such an organisation might be an issue since ECs are used to work through regular (generally monthly) meetings as a voluntary basis and not as full-time jobs.

Thus France supports the principle of keeping separate NCAs and ECs assessments, although we recognise the need to further develop respective exchanges of information. The communication between the 2 bodies could be further detailed in the legislation.
Ethical and local issues of CTAs are to be managed at the national level.
France agrees that each MS concerned should be responsible of the final decision about CT. This national decision has to take into account assessment of a), b) and c) parts of the dossier. In this way, the CT directive should clearly indicate that MS has to refuse CT if one part of the dossier (a, b or c) obtained a negative assessment (from the CAP or from national Ethic committee).

1.3.1. Scope of the CAP

According to the Commission a CTA assessment is composed by 3 areas:
"a). the risk benefit assessment as well as aspects related to quality of the medicines and their labelling.
b). ethical aspects related to informed consent, recruitment and reward
c). local aspects related to suitability of sites, the investigator and national rules".

According to the Commission, the joint/coordinated assessment of a CT should only cover issues described in section a) such as the benefit/risk assessment and aspects related to quality of the medicines and their labelling, including

- "acceptability of the clinical trial in view of all anticipated benefits, compared to risks and inconveniences for trial subjects (including control group), taking account of
    - the characteristics of and knowledge about the investigational medicinal product,
    - the characteristics of the intervention compared to normal clinical practices;
    - the design of the trial;
    - the relevance of the trial, including the credibility of the results;
- compliance with the requirements for manufacturing labelling and importation of the medicinal products intended for the clinical trials;
- completeness and adequateness of the investigator's brochure".

Issues relating to section b)ethics (e.g. completeness and adequateness of informed consent, arrangement for recruiting subjects and compensation of subjects and investigators) and to section c)local issues (e.g. suitability of investigators and of CT sites, insurance and indemnisation, compliance with rules on personal data protection) would be within the remit of MS.

Consultation item no. 4: Is the above catalogue complete?

France thinks that further details or clarification should be given about the assessment of the methodology and the statistical considerations of the protocol which are not clearly identified.

Also we think that the risk assessment should not be limited only to investigational medicinal products (IMP) but also to the auxiliary medicinal products and medical devices (where they are not EC marked) to be used in the CT and the trial related procedures.

As the investigator's brochure may be replaced by other documents in accordance to the CT1 guidance, the wording should be reviewed.
The protocol is also to be clearly listed in the coordinated assessment since inclusion/exclusion criteria, stopping rules, choice of dose, subjects monitoring and risk mitigation strategies are to be assessed in common in the benefit/risk evaluation.

Regarding ethics, the procedure to be followed for obtaining informed consent and the justification for the research on person incapable of giving informed consent should be added. The relevance of the trial and whether the evaluation (by the sponsor) of the anticipated benefits and risks is satisfactory should be also an ethical issue and listed in section b).

Consultation item no. 5: Do you agree to include the aspects under a), and only these aspects, in the scope of the CAP?

France thinks that the joint assessment should be focused on the risk-benefit assessment of the CT based on quality and safety of medicines being used in the CT and safety of the subjects in the trial, taking into account:
- knowledge about quality, efficacy and safety of the medicinal products intended for the CT (MP),
- conditions of use of the MP and the risk mitigation strategies in the protocol
- the interventions other than MPs in the trial, compared to normal clinical practice
- the protocol and the information available on medicinal products (IB or equivalent)
- the methodology, the trial design, the credibility of the results and statistics.

We think that this joint assessment should be performed generally by the NCAs of the MS concerned through the CTFG, giving the CTFG a legal basis.

We also believe that a procedure in case of second wave of applications should be drawn up with the objective that the initial coordinated assessment is taken into account.

1.3.2. Disagreement with the assessment report

In the CAP, the Commission proposes 3 ways to deal with disagreements among MS:
- either by opting-out if justified by serious risk to public health or subjects safety,
- or by vote by MS concerned with a decision based on the majority
- or by referring the matter to the Commission or EMA for a EU decision.

Consultation item no. 6: Which of these approaches is preferable? Please give your reasons.

France thinks that opting out only for serious risk to public health or safety of the participant is not logical in the CAP as defined by the Commission (in that situation of serious risk for public health, all the MS should take the same position). However we think that in the CAP the only option for a MS who does not agree with the other MS and who has major objections is to opt out.
We believe that it is the responsibility of the RMS to reach a consensus between the MS concerned.

Indeed, the CAP should not allow national specificities and avoid the situation where the same CT has different national version/applications in EU (not il line with the multicentre trial definition).
The 2 other options are not appropriate: arbitration at EMA level as EMA is not in charge of CT assessment and decision and vote by majority would not be acceptable for that MS who has major concerns.

1.3.3. Mandatory/optional use

Consultation item no. 7: Which of these three approaches is preferable? Please give your reasons.

France believes that CAP should be mandatory for all CTs in order to give a clear picture of the EU system with a single process.
This would be of importance for multinational CTs.
It is also the best way to achieve harmonisation and simplification.
It should simplify the situation where a second wave of countries are involved in the trial

1.3.4. Tacit approval and timelines

This section covers several aspects:
- The tacit approval would not be possible under the CAP and explicit authorisation by MS would be mandatory
- Timelines for CTA should not be as a general rules 60 days and time lines for substantial amendments should be fixed.
- Timelines should be shortened for some CTs (the type A trials) where the risk for subjects is low compared to normal clinical practice
- A definition of type A trials is proposed
- Type A trials would be identified in a pre-assessment.

Consultation item no. 8: Do you think such a pre-assessment is workable in practice? Please comment.

- Timelines in 60 days are acceptable for Afssaps in assessing section a) of the CAP. Considering the ethical and local assessment (b + c) that would be certainly performed by ECs in parallel, 60 days would not allow any clock stop and this is maybe not workable for ECs, due to their organisation based on meetings.
  Fixing timelines for significant amendment (SA) is also a good proposal, as it is currently laid down our of national legislation.
- Shortening time lines for “low risk” clinical trials (type A) is also supported but those timelines should be clarified.
- The idea of pre-assessing the classification as type A CTs is acceptable but might need further clarification such as : who does the pre-assessment and when. We also emphasise the need for harmonisation of such classification in EU.

France proposes that:
- The sponsor justifies in the CTA its own classification
- The CTFG is in charge of this assessment
- This classification is reviewed on a case by case basis by the CTFG in order to ensure harmonisation

- Time lines for classification are included in the CAP timelines
- A pilot phase is set up as soon as possible on a voluntary participation basis.

Regarding the definition of type A CTs we think that it should be aligned to the other current reflexions (OECD, FDA …) and we strongly suggest that :
- "indication" is replaced by "conditions"
- "a" MS by "the" MS.

2. BETTER ADAPTATION TO PRACTICAL REQUIREMENTS AND A MORE HARMONISED, RISK-ADAPTED APPROACH TO THE PROCEDURAL ASPECTS OF CLINICAL TRIALS

2.1. Limiting the scope of the Clinical Trials Directive

2.1.1. Enlarging the definition of 'non-interventional' trials

Commission Preliminary appraisal: Rather than limiting the scope of the Clinical Trials Directive through a wider definition of 'non-interventional trial', it would be better to come up with harmonised and proportionate requirements which would apply to *all* clinical trials falling within the scope of the present Clinical Trials Directive. See in particular points 2.2 to 2.5.

Consultation item no. 9: Do you agree with this appraisal? Please comment.

Position from France is the following:

France considers that the scope of the Clinical trial directive should not be limited by a wider definition of 'non-interventional trial'.
As a reminder, European regulations and texts dealing with 'non interventional trials' are the followings:
- Clinical Trial Directive 2001/20/EC, (Article 2(c) 10), which provides a clear definition: "A study where the medicinal product(s) is (are prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within the current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data".
- Annex 9 of the directive 2001/83/EC, now obsolete, stated that "In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice. Based on these definitions a fundamental distinction can be made between non-interventional (observational) and interventional post-authorisation safety studies. The latter are considered clinical trials falling under the scope of the Directive 2001/20/EC".
- Article 107 quaterdecie, laying down provisions for Non interventional Post-authorization Safety Studies.

France strongly supports the principle of proportionality of the provisions for CT on a risk-based approach rather than enlarging the scope of non interventional studies.
Revision and adaptation of the provisions should concern:

- carry on and clarification of harmonized and proportionate requirements which would apply to *all* clinical trials falling within the scope of the present Clinical Trials Directive (See in particular points 2.2.).
- revision of the last part of the definition (epidemiological methods) should be discussed as it does not seem to match a recognized usual definition.
- explanation on Current practice and current diagnostic or monitoring procedures in a non binding document (see § 1.9. of the Questions and Answers document).

(This does not preclude proposal for general principles for good practices of non interventional studies on medicinal products, which should be established in other regulatory texts.)

2.1.2. Excluding clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

Consultation item no. 10: Do you agree with this appraisal? Please comment.

Commission Preliminary appraisal: Rather than limiting the scope of the Clinical Trials Directive, it would be better to come up with harmonised and proportionate requirements for clinical trials. These proportionate requirements would apply independently of the nature of the sponsor ('commercial' or 'academic/non-commercial'). See in particular points 2.2 to 2.5.

France agrees that academic clinical trials should remain covered by the clinical trials directive in order to ensure the same level of protection of subjects and the same level of reliability of data.

2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Commission Preliminary appraisal: This approach would help to simplify, clarify, and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, risk-adapted set of rules.

Consultation item no. 11: Do you agree with this appraisal? Please comment.

Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?

Position from France is the following:

Consultation item n° 11: France supports the need to establish proportionate requirements based on the risk. The followings should be taken into account in order to consider the foreseeable risk of a clinical trial:

. The risk to trial subject safety compared to normal clinical practice

This involves:

. the risk of the investigational medicinal product

. the risk of the trial related investigations

. The risk to data reliability and robustness, and the consequence of this risk in terms of public health .

Consultation item n° 12: France considers that following aspects should be the subject of specific provisions:

. the content of the clinical trials application dossier,
. rules for safety reporting
. traceability system for investigational medicinal products
. monitoring procedures by the sponsor
    . monitoring by sampling, % of data reviewed
    . ratio central / on site monitoring

2.3. Clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Commission Preliminary appraisal: This combined approach (new definition for the 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products') would help to simplify, clarify, and streamline the rules for medicinal products used in the context of a clinical trial.

Consultation item no. 13: Do you agree with this appraisal? Please comment.

Position from France is the following:

Definition of IMP: The current definition of IMP, laid down by Article 2(d) of Directive 2001/20/EC is the ICH E6 guidance definition. This definition raised divergent interpretations for the products with a marketing authorisation when used or assemble in the respect of the approved form and approved indication. The placebo is not mentioned in the proposed definition, then France proposes: '*A pharmaceutical form of an active ingredient or placebo which is tested or used as a reference in a CT.*'

'Auxiliary medicinal products', covering all other medicinal products used in the context of the clinical trial:
- must be introduced.
- The definition could be '*A medicinal product as referred to in Article 3(3) of Directive 2001/83/EC, which is not an investigational medicinal product and which is provided by the clinical trial protocol*';

'Auxiliary medicinal products' should be subjected to a proportionate regulatory regime, which would be separate from IMPs; and

The rules for dossier requirements, reporting, and labelling for both IMPs and auxiliary medicinal products should be set out in the Annex to the basic legal act.

2.4. Insurance/indemnisation

Commission Preliminary appraisal: Both following policy options could be a viable solution.

. Removing insurance/indemnisation requirements for low-risk trials: This policy option would remove the insurance requirement for clinical trials which typically pose a low risk for trial subjects
(see point 1.3.4); or

. Optional indemnisation by Member State: This policy option would put Member States under an obligation to provide for an indemnisation for damages incurred during clinical trials performed in their territory, taking account the national legal system for liability. In view of the damages arising today (see annex), the burden on national budgets would be minimal.

France does not support the first option, even for clinical trials with low risk, considering that the need for insurance must remain as a principle for all clinical trials, as a guarantee of protection for all subjects enrolled in clinical trials. Instead, it is proposed that each Member State should seek to reduce constraints of insurance policies for type A clinical trials within their national legal system.

Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

2.5. Single sponsor

The Clinical Trials Directive is based on the concept of a 'single sponsor' per trial. The single sponsor is 'responsible' for the trial vis-à-vis the national competent authority and the Ethics Committee.

It is a recurrent criticism that the concept of a 'single sponsor' renders multinational clinical trials more onerous.

Commission Preliminary appraisal: In view of the above, option 1 (maintaining the concept of a single sponsor) may be preferable, provided that:
. it is clarified that the 'responsibility' of the sponsor is without prejudice to the (national) rules for liability; and
. it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised (see point 2.2).

Consultation item no. 15: Do you agree with this appraisal? Please comment.

Position from France is:
When a clinical trial sponsor implies several actors, it is important that the directive simplifies the difficulties created by such organization for competent authorities and ethics committees and moreover for the persons participating in it. That is the reason why the directive has to protect the persons by identifying only one legal person in charge on the community territory, the sponsor.

The consultation paper highlights the confusion made by stakeholders between 'responsibility' for the trial and 'liability' vis-à-vis the trial subject in case of damage. See art 2(c) and 19 of CT directive, art 7.1 of directive 2005/28/CE).

Regarding the definition of the sponsor and its responsibilities, France supports that an organisation including different parties and presenting:
. pre-established contractual arrangements for the management of the different trial related activities,
. a set of SOPs describing duties of the different trial parties, circuits and timelines for information and data
is acceptable.
This organisation is the sponsor. The concept of one single sponsor is highly preferable.

2.6. Emergency clinical trials

Commission Preliminary appraisal: This could be a viable option in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts.

Consultation item no. 16: Do you agree with this appraisal? Please comment.

Position from France is:

The consent is an essential element for ensuring the protection of persons participating in a clinical trial. That is why, France strongly supports that the Clinical Trials Directive specifies the conditions of implementation of emergency clinical trials according to the international texts (Declaration of Helsinki of the World Medical Association, the Convention on Human rights and Biomedicine of the Council of Europe, and the Guidelines on Good Clinical Practice of the International Conference on Harmonisation, 'ICH'). All these texts explicitly address the issue of emergency clinical trials: some clinical trials answering strict criteria could be realized without preliminary consent of the interested or a free designated person to be the interlocutor of doctors when the person is not able to express his/her choices.

In view of these texts, the Clinical Trials Directive should be amended to the effect that the informed consent and the information from the investigator may take place during or after the clinical trial under the following conditions examined by ethics committee. These provisions take into account current provisions of Article 5 of Directive 2001/20/EC:

- such trial is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods
- the trial relates directly to a life-threatening or debilitating clinical condition from which the CT subjects concerned suffers;
- clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored;
- the Ethics Committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;
- the interests of the patient always prevail over those of science and society; and
- there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risk or will produce no risk at all.
- The trial subject is not in a state to give informed consent;
- The physical or mental conditions that prevents giving informed consent is a necessary characteristic of the research population;
- Because of the urgency of the situation, it is impossible to obtain informed consent from the parents (in addition to any other relevant restriction within clinical trial on minors)/legal representative (in case of adults) in accordance with the Clinical Trials Directive, and it is impossible to give the information, as provided in the Clinical Trials Directive;
- The trial subject has not previously expressed objections known to the investigator.

In this case, the informed consent would have to be obtained as soon as possible from the parents/legal representative (in case of adults) or the trial subject, whichever is sooner. The same holds for the supply of information to the trial subject.

3. ENSURING COMPLIANCE WITH GOOD CLINICAL PRACTICES IN CLINICAL TRIALS PERFORMED IN THIRD COUNTRIES

Preliminary appraisal: In view of the jurisdictional limits, particular consideration should be paid to clinical trials in third countries where the data is submitted in the EU in the framework of the authorisation process of
. Clinical trials; and
. Medicinal products.

Regarding the authorisation process for a clinical trial
. Codifying, in the revised legislative framework, the provision in point 2.7.2.4.of the detailed guidance CT-1 (statement of GCP compliance and reference to the entry of this clinical trial in a public register) ;
. Further supporting capacity building in third countries where the regulatory framework for clinical trials, including its enforcement is weak.
. In addition, in order to increase transparency of clinical trials performed in third countries the legislation could provide that the results of these clinical trials are only accepted in the context of a marketing authorisation process in the EU if the trial had been registered in the EU clinical trials database *EudraCT* and thus be published via the public EU-database *EudraPharm*.(20)

Consultation item no. 17: Do you agree with this appraisal? Please comment.

Position from France is:
. Agreement on the codifying in the revised legislative framework, the provision in point 2.7.2.4.of the detailed guidance CT-1 (statement of GCP compliance and reference to the entry of this clinical trial in a public register) ;
. An obligatory commitment by European sponsors to apply GCP in clinical trials performed in third countries
. Provisions for assessment by M.S. Ethics Committees, on a voluntary basis, of clinical trials conducted in third countries.

4. FIGURES AND DATA

Enclose are some figures regarding CTs in France in 2010 (excluding cells and gene therapies):
- 903 CTAs (excluding resubmissions/n =38)
- Mean time for CT authorisation by Afssaps : less than 40 days (including recevability ; no clock stop in France) (mean time is 35 days if resubmissions are included)
- More than 30% are authorised in less than 30 days
- 1609 substantial amendments for authorisation ; mean time for authorisation: less than 21 days
- 48 742 SUSARs (initial + follow up reports ; domestic and abroad) ; 1095 annual safety reports, 130 other safety issues.
- Current resources at Afssaps dedicated to CT assessment (FTE) :
  - One Head of CT unit
  - CTA medical assessors : 6.8
  - CTA non clinical assessors : 1.3
  - CTA pharmaceutical quality assessors : 1.3
  - CTA validation assessors and project managers : 3.9
  - CT regulatory affairs 0.8
  - SUSARs and other safety issues: 1.6

- ASR: 1

5. OTHER ISSUES TO BE COVERED BY THE REVISION OF THE DIRECTIVE

5.1. The management, the assessment and the decision making process regarding CT safety issues are not mentioned/discussed by the Commission in the concept paper. France believes that it is a major field regarding public health protection and which needs also simplification and harmonisation of processes, coordination of assessment and decision and better use of resources, that should be strongly discussed in the revised legislation. There is a need for:

- a single repository for development safety update report (DSUR) and notification of the development international birth date (DIBD)
- a safety assessment coordination by the CTFG and harmonisation decision
- an improvement of EVCTM to allow MS to follow SUSARs of interest (the Commission is invited to take consideration of the CTFG/NCAs needs developed in a report to EMA/Com. In 2010)
- a revision of safety reporting rules to Ethics Committees
- a clear definition of roles of NCAs and ECs on the safety topic.

5.2.Provisions for a public register of clinical trial information (transparency on trials and inspection outcome)

5.3. A clear reference to international GCP (ICH)

5.4.Provisions on serious breaches of GCP/trial protocol provisions

There should be provisions:

- regarding the obligation for reporting serious breaches of GCP/trial protocol provisions by sponsors or CROs or any stakeholder
- for publishing the results and consequences of inspection regarding legal enforcement : investigator ineligibility, list of non compliances (Amendement of Article 12 of Directive 2001/20)

5.5.Provisions on capacities of stakeholders (sponsors/CROs/investigators)

Provisions on capacities are vague in the different texts, there is no provision in Directive 2005/28/EC and some countries implemented provisions for investigators and CROs in terms of organization, training… A basic set of provisions should be implemented in the future Directive.

5.6. Provisions on manufacturing / distribution of IMPs

The current version of the Directive voluntary did not provide provisions on the distribution from the manufacturer / importer. Possible flexibility proposed for labelling and characteristics of post marketing safety studies will certainly imply new actors in clinical trials (street pharmacies) and requirements for such sites should be discussed.

To finish, french authorities underline the necessity to control trials versus placebo and versus an established medicinal product of proven therapeutic value

Surrounding the « Médiator affair », the French health minister Xavier Bertrand has expressed several times his willingness to change the rules for granting the Marketing Authorisation (MA) at a European level.

The binding request “controlled trials versus placebo and versus an established medicinal product of proven therapeutic value” is in the annex to the amended 2001/83 directive. Every other ways to proceed has to be justified. However many current MA are obviously granted without any MA application allowing to assess the BRR of the studied medecine versus the relevant alternative. This is due to the definition of the grounds for MA refusal within the

amended 2001/83 directive. A MA is refused if “the medicinal product is harmful in the normal conditions of use”. Any clear reference to medicines whose therapeutic value is already commonly known is not mentioned.

In the frame of the CHMP consultation on the “reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available – March 2011” France (Afssaps) has already expressed its willingness that the standard used for MA should be based on a double requirement (1) superiority to placebo added to (2) a conclusion of the absence of substantial worsening of its benefit risk balance as compared to existing drugs, so that it can be a priori considered that the basic health interests of the patients should not be substantially harmed by this drug.

Within its Conclusions on Innovation and Solidarity in the field of Pharmaceuticals in December 2010, it might be recalled that the Council has invited the European commission and the member states to revise the clinical trials directive in dialogue with the European Parliament, with the aim of ensuring an improved regulatory framework for developing medicinal products and comparing alternative treatments with medicinal products in clinical research.

The French proposal is then to introduce within the Directive, the following paragraph:

When controlled clinical trials are aimed at applying for a Marketing authorisation of medicinal products, the treatment of the controlled group should include a relevant medicinal product of proven therapeutic value in order to provide sufficient data to demonstrate that the experimental medicine is not harmful compared to any established medicinal product.