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Assessment of the functioning of the « Clinical Trials Directive » 2001/20/EC

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Sanofi-aventis and Sanofi Pasteur response

L'essentiel c'est la santé.

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Consultation item n°1: Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of Clinical Trials Directive?

Overall, sanofi-aventis considers that one of the key objectives of the Clinical Trials Directive "*Protection of the health and safety of clinical participants*" has been achieved. As far as the protection of patients is concerned, the nature/stringency of the requirements and obligations should not be driven by the status/identity of the sponsor.

The Clinical Trials Directive has established a common European legal basis for the implementation of Good Clinical Practice ("GCP") in the conduct of all clinical trials on medicinal products for human use.
GCP were previously an established standard only, and did not cover clinical studies conducted outside registration purpose. GCP were strongly recommended for clinical trials for registration purpose only. As Directive 2001/20/EC applies to all interventional studies, clinical trials with no registration purpose are also concerned.

Investigator sponsored clinical trials (IST) / Investigator-driven clinical trials (IDCT) being in the scope of Directive 2001/20/EC are conducted according the same requirements mainly ensuring good protection of patients and a consistent implementation of GCP.

Also, electronic reporting of SUSARs to Eudravigilance and submission to the National Competent Authority (NCA) and Ethics Committee (EC) of an Annual Safety Report (ASR) describing safety information received during the reporting period are examples of Directive 2001/20/EC requirements that can improve the protection of subjects and patients receiving investigational medicinal products.

Eudravigilance

The reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) during clinical trials is defined in Directive 2001/20/EC [Article 17(1)(a) and (b)]. As required in Articles 17(3)(a) and 11(1) of the Clinical Trials Directive, a European database - The Clinical Trial Module (EVCTM) of Eudravigilance - was created to facilitate the electronic reporting of SUSARs and the review of the safety of the products used in clinical trials conducted in the Community.

While the reporting of SUSARs to EVCTM still needs to be harmonised (*see response on consultation item n° 6*), the concept of a single database to receive all SUSARs is a good example of improved protection of clinical trial participants.

This database is accessible only to all NCAs, the Commission and the Agency and:

- Provides an overview of SUSARs in all clinical trials in the Community
- Facilitates communication between NCAs , the Commission and the Agency on SUSARS
- Can be used to detect signals
- Can ensure consistency of important information to review safety data in specific populations, group of products or therapeutic areas through common fields with European clinical trials database (EudraCT) such as the clinical trial identification, product identification and sponsor identification.

Annual Safety Report (ASR)

The requirement for an ASR to be submitted to NCA and EC in whose territory the clinical trial is being conducted is set-out in Article 17(2) of Directive 2001/20/EC. Content and reporting time frame are described in the European Commission detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT 3 revision 2, April 2006).

While the content of the ASR still needs to be harmonised throughout the Community and improved (e.g. by incorporating cumulative summary tabulation as recommended in the upcoming ICH guideline E2F Development Safety Update Report), its implementation has provided NCA and EC where clinical trials are conducted with additional aggregate safety information relevant to the concerned clinical trials and assessment of the conditions of patients actually included in the clinical trials.
In addition, the very recent harmonisation of the 7/15 days SUSARs reporting timelines as well as the ICH E2B format for electronic transmission of Individual Case Safety Reports (ICSR) reporting works well and as such contributes to the protection of patients/subjects enrolled in clinical trials.

However the others purposes of the Directive 2001/20/EC were not attained such as "*Simplification and harmonisation of the administrative provisions governing clinical trials in order to allow for cost-efficient clinical research*".

Consultation item n°2: Is this an accurate description of the situations? What is your appraisal of the situation?

Sanofi-aventis believes that it is necessary to streamline the Clinical Trial Authorisation (CTA) process:

- **Identify the respective responsibilities for NCAs and ECs**
- **Implement an optional centralised pathway for authorisation of multinational trials**

Sanofi-aventis considers that it is an accurate description of the situation.

a) The lack of harmonisation is illustrated by various requests from NCAs and ECs. Some examples:
   - Annexes have to be appended to the protocol in order to cover specific national requests concerning contraception measures that were valid in only some EU countries.
   - Specific requirements and questions regarding clinical trials with pharmacogenetic sub-studies.
   - Specific national rules on the Informed Consent Form to guarantee a limited access to patients' data especially when biological samples and pharmacogenomics data are requested.

b) The lack of harmonisation is illustrated by divergent approaches and conclusions on the assessment of the same clinical trial between:
   - NCA & EC in the same country
   - Local EC & Central EC in the same country
   - Several Member States

   - NCA & EC in the same country

     We experienced divergent opinions between NCA and EC. For instance, one protocol was first approved by the NCA but then EC rejected the study because the safety & efficacy of the active comparator was considered uncertain. Afterwards, the CA reverted its decision based on the EC opinion. Therefore, the CTA was withdrawn and the study was not implemented in this country whether it continued as planned in nine other EU countries.

     Interestingly, NCAs sometimes give divergent opinions concerning the same type of studies. For instance a study with an anti-diabetic vs. placebo with a treatment of 3 months has been refused by a NCA but some months later a similar study with the same anti-diabetic vs. placebo with a treatment of 1 year was approved.

   - Local EC & Central EC in the same country

     In some countries, Local ECs raise additional questions on the protocol after it has been evaluated by the Central EC. Sponsor's answers are reviewed at the next Local EC session increasing the review timelines and the workload both at sponsor and EC level. In some cases real duplication of efforts is observed.

   - Several Member States

     We experienced in many instances difficulties with the categorisation of Investigational Medicinal Product (IMP) or Non-Investigational Medicinal Product (NIMP). In a multiple sclerosis study comparing one novel entity vs. placebo with interferon as a background treatment, interferon was not accepted as background treatment in some EU countries which led to the withdrawal of the CTA in these two countries.

     We experienced difficulties with regard to the use of placebo as well as the duration of the comparative period.
     A placebo-controlled study has been approved in seven EU countries, but refused in one country due to the use of placebo.
     On the same phase III development program, one MS approved a study placebo-controlled with a treatment of 1 year, whereas another MS refused a similar study placebo-controlled with a treatment of 6 months, the duration being the reason of the refusal.

We experienced also protocol amendment valid in only one country. It happened that in a study in diabetes, one country out of 8 refused to approve a study unless we agreed to limit the type of treatments used as concomitant treatments in the same patients.

c) The lack of harmonisation can be illustrated in the definition of IMP or NIMPs between MSs.
In one MS, the same product did not meet criteria for NIMP accepted in other MSs, so it had to be re-classified as IMP and additional information had to be submitted by sponsor. Consequently the application form submitted to EudraCT contained more IMPs in one country than in the other countries for the same study.

Also, a same study has been considered as a phase I study in one country and not under the scope of the Clinical Trials Directive in another country.

- *In the 1st country, a study was conducted with only administration of NIMP to subjects. This NIMP was a challenge agent to produce a physiological response to assess the pharmacological action of an IMP in a subsequent study. This study was considered as a study under the scope of the Clinical Trials Directive and a CTA had to be submitted to both EC and NCA.*
- *In the 2nd country, a similar study with administration of NIMP (challenge agent) was not considered as study under the scope of the Clinical Trials Directive because no IMP was administered. This study had to be submitted only to EC for review.*

d) The lack of harmonisation is illustrated in the classification of amendment as substantial or non substantial (*see response on consultation item n° 6).*

Consultation item n°3: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

A predictable timeframe consistent across MSs is a need if the EU Community wants to achieve that pivotal multinational trials are effectively implemented in the EU, with respect to other Regions.

Sanofi-aventis considers that it is an accurate description of the situation.

- **Resource & Cost:** Sanofi-aventis set up dedicated teams both at corporate and affiliate levels to manage the CTA process. Multiple submissions and the consequent various additional national requests are very time and resource consuming. We also consider that these difficulties can discourage small and medium enterprises and investigator sponsored clinical trials.

- **Delays in review timelines:**
  - Validation period (3 to 10 calendar days) not included in the review timelines in approx. 12 countries
  - Need to get "appointment" to submit CTAs in some countries
  - Fixed submission dates
  - Due to unclear NCA request, we experienced the need for up to 3 submissions of the same amendment in the same country until we managed to provide the desired level of details for a track change document. This led to a delay of 63 days in the start of the evaluation.

- **Patchwork of separate assessment procedures:**
  We experienced the situation in one country where the EC refused to provide opinion unless a full IMPD was submitted to EC although it was not necessary for evaluation.

  Approval timelines and submission process are also very different from one country to another: They vary from 12 to 108 calendar days for phase II & III.

  In four MSs, parallel submission to NCA and EC is possible, but in practice EC opinion is needed before NCA approval is released.

  In some MSs, outcome of the evaluation of a previous CTA with the same product allows a shorter CA approval timelines for a subsequent CTA with the same product. This logic could be extended to all countries.

Consultation item n°4: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

Sanofi-aventis believes that an optional community authorisation would be very beneficial. By using scientific expertise of the EMEA, this will result in high level of continuity in the dialogue with the regulators during the development and life cycle of medicinal products.

We fully support the EFPIA position:

"A Community approval system would by necessity need to be coordinated and managed centrally. The proposed procedure should be managed by an existing structure, i.e., the EMEA, rather than through establishing some new European body or institution."

"The new procedure should be optional in nature and operate in parallel within the existing national CTA approval system. The optional character should cover the right to switch from one approval systems to the other at different stages of development. We believe the new procedure should not be limited to any particular category of product or therapeutic area."

Consultation item n°5: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

An improvement could be reached by applying the current Clinical Trials Directive concept of one unique Central Ethics Committee opinion per Member State.

In fact, several countries have not implemented the Clinical Trials Directive according to this principle. Sponsors need to obtain several approvals from multiple local ECs in addition to national/regional EC in the same Member State in most EU countries. This organization has a negative impact on consistency of EC decisions and timelines.

Concerning the proposed options, we consider that option 3.4.1 would be a good solution but not realistic. A proposed solution would be a combination of option 3.4.2 and option 3.4.3 i.e.:

- Clarify and harmonise the respective roles of NCA and EC. We suggest the scientific evaluation and quality of IMP for the NCA scope of evaluation, and ethical consideration, protection of patients and site qualification for the EC scope of evaluation.
- Reinforce the recommendation for one central EC in any Member State.
- Clarify the respective roles of Central/Regional EC versus Local EC if the latter is considered needed (e.g. role of Local EC limited to site qualification).
- Harmonise the evaluation procedure across Member States.

KEY ISSUE N° 2 TO BE ADDRESSED: INCONSISTENT IMPLEMENTATION OF THE CLINICAL TRIALS DIRECTIVE

Consultation item n°6: Is this an accurate description of the situation? Can you give other examples?

Sanofi-aventis believes that the inconsistent implementation of the Clinical Trials Directive is the main cause of failure with regard to the objective of "*Simplification and harmonisation of the administrative provisions governing clinical trials in order to allow for cost-efficient clinical research*".

Substantial Amendments

Sanofi-aventis believes that a harmonized and comprehensive list of substantial amendments would be beneficial to increase clarity and therefore reduce overall number of substantial amendments.
Also we consider that when a substantial amendment is to be evaluated by only one body (NCA or EC), it should be acceptable to submit it for information to the other body only once it is approved by the first body.

There is no clear application and interpretation of the definition for substantial amendments. Each change needs therefore to be discussed for arbitration between EU legislation and local legislations before submission. This led to over-submission of amendments.

- Non substantial amendment: In some countries, non substantial amendments are to be "notified" (submitted) for information. This is in contradiction with the Clinical Trials Directive.
- Substantial amendment: Since there is no precise definition, a conservative approach is sometimes chosen as almost all changes can eventually be interpreted as having influence on the safety of the participants.

Here are examples of un-harmonized substantial amendments:

- In some MSs, the Investigator Brochure (IB) annual update is to be submitted to NCA whatever benefit/risk ratio changes are. In other MSs, the IB annual update should only be submitted in case the benefit/risk ratio is impacted.
- In some MSs, the extension of shelf-life should be submitted to NCA for authorisation, other MSs consider it is the sponsor responsibility to guarantee the validly of IMP and do not want to receive extension of shelf life information.
- In some MSs, if the planned number of subjects in the concerned MS changes (but no change for the planned number of subjects in the Community and in the entire clinical trial), this change is to be submitted as substantial amendment for authorisation in some countries and for information or not submitted at all in others.

Reporting of SUSARs

Sanofi-aventis believes that streamlining safety reporting (via single SUSARs reporting to EudraVigilance) is essential for avoiding double reports for saving time and resource both at the level of sponsor and NCAs and most of all will increase the accuracy of collected safety data.

Responsibilities of the sponsor with regards to reporting of SUSARS are set out in Article 17 of the Clinical Trials Directive:

- Article 17 (1)(a) and (b) provides for the expedited reporting of SUSARs to the NCA and EC
- Article 17 (1)(d) states that the sponsor shall also inform the Investigators
- Article 17 (3)(a) sets out that SUSARS should be entered in a European database and that "*Each member state shall see to it*".

Sponsor's responsibilities have subsequently been detailed in two implementing guidelines published by the European Commission in EudraLex Volume 10 Clinical Trials guidelines (ENTR/CT 3 revision 2, April 2006 and ENTR/CT 4 revision 1, April 2004).

The meaning of the phrase "*Each member state shall see to it*" which has been interpreted inconsistently within NCAs together with the lack of clarity of the two implementing guidelines have led to:

- ***Confusion with regard to the role and responsibilities of each stakeholder*** which may explain the over-reporting to Eudravigilance noticed in the ICREL report Impact on clinical research of European legislation (February 2009); in particular, the SUSARs reporting by NCAs to EVCTM while others leave this reporting to the sponsor.

- ***Inconsistency in national requirements for SUSARs reporting to NCAs by sponsor***, e.g.:
  - Local SUSARs only
  - Local and foreign SUSARs (occurring within or outside the EEA, occurring within the same CT or within another CT testing the same IMP)
  - No safety reporting requirement by NCAs which can look at the information in EVCTM
  - Electronic reporting not yet implemented by all NCAs. Reporting under paper format still requested by some NCAs
  - 7-day rule for Death/Life threatening events applied to spontaneous SUSARs with a marketed product also studied in the same country
  - Duplication of case reports into Eudravigilance
  - Inconsistent and insufficient population of information on IMPs in EV Medicinal Products Dictionary (EV MPD) by NCAs and sponsors

- ***Other examples of inconsistent safety reporting***
  - Additional expedited reporting requirements exist in some countries (expected serious reactions).
  - Notification to ECs: Lack of harmonization between the requirements of NCA and ECs observed in some countries and across countries:
    - Local SUSARs vs. Local and Foreign
    - Not all MSs/NCAs allow the practice of periodic line-listings for notification to ECs
  - Notification to the Investigators: Differences are also observed between countries
    - Expedited all SUSARs
    - Expedited local and periodic line listing for Foreign SUSARS
    - Periodic line-listings only
  - Annual Safety Report:
    - Different requirement in the content or format of ASR between countries
    - Additional specific requirements in some countries (e.g. listing of all local SAEs + number of patients enrolled in the study conducted in the country)
    - Lack of harmonisation with regards to the submission of the report and the end of the study
    - Clarification with regards to the 90-day report for short term studies

Scope of the Clinical Trials Directive

The scope of the Clinical Trials Directive should clearly only apply to "interventional trials" with administration of IMPs, not to so-called "non-interventional" trials.

The Clinical Trials Directive is restricted in scope to interventional trials. The problem, as outlined below, is not the scope definition in the Directive but its application and interpretation. According to the MSs, some studies which are non-interventional regarding the product prescription may fall within the scope of the Clinical Trials Directive.

The main problem is the definition of non-interventional studies. Our proposal would be to define the scope of the Clinical Trials Directive as limited to clinical studies, which are **interventional on product prescription**. All other programs should be outside the Clinical Trials Directive and could be name non-interventional on product prescription/observational.

We consider that a clinical observational study where the main objective is patient follow-up (including ad hoc tests) during independent prescription by the physician is not an interventional trial and should be outside the scope of Clinical Trials Directive. On the other hand any study testing the efficacy/effectiveness of a given product (including already marketed ones) is an interventional clinical trial.

We propose to amend the definition provided in Directive 2001/20/EC for non-interventional study. Based on Directive 2001/20/EC, in a non-interventional study the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study.
We propose to delete from this definition the following: "~~*No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data*~~."
Indeed this sentence may be inconsistently interpret and conduct some NCAs to inappropriately apply the Directive 2001/20/EC to non-interventional studies on product prescription/observational. This modification would avoid current inconsistency (in classification) between NCAs.

For non-interventional on product prescription/observational, there is a **need** for detailed guidance as:
- More and more, Marketing Authorisation Holders are requested to provide « real life data », coming from non-interventional/observational studies (e.g. studies proposed to support Risk Management Plan)
- No harmonisation at all exists for the conduct of such studies creating inconsistencies and no secure patient protection

Guidelines exist for a part of these studies in EudraLex Volume 9 for Post-Authorisation Safety Studies (PASS). ICH-guideline E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting could be also considered as a reference for pharmacovigilance.

However, except for data protection aspects (Directive 95/46/EC) and for pharmacovigilance aspects (Volume 9 and ICH E2D), no harmonised regulatory framework exists. Due to the lack of well-defined legislation, some NCAs apply Directive 2001/10/EC to non-interventional studies on product prescription/observational which leads to real difficulties as it is not adapted at all. This approach could help to solve some issues on risk differentiation approach issues (*see response on consultation item n° 9*).

The **draft Code of conduct of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)** recently published by the EMEA (EMEA/489873/2008) for public consultation can be a relevant guideline for such studies.

Consultation item n°7: Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Sanofi-aventis believes that it is necessary to streamline the Clinical Trial Authorisation (CTA) process and the supervision of clinical trials.

Sanofi-aventis considers that it is an accurate description of the situation.

- **Increase of administrative costs:** The divergences in the implementation of the Clinical Trials Directive (without scientific rationale) have created a considerable increase in administrative burden and costs for sponsors. The lack of harmonisation in the requirements of the NCA, ECs and the Investigators between the countries has led to a very complex configuration and heavy maintenance of reporting rules in pharmacovigilance database to ensure compliance with safety reporting obligations, without any expected benefit for the patient.

- **Insufficient patient protection:** Over-reporting and duplication of reports to EVCTM may lead to unreliability of safety data and mistakes in signal detection.

Consultation item n°8: Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis?

For reasons of public health, legal consistency, reducing the administrative burden and strengthening predictability for economic operators, clinical trials should be subject to harmonised rules. **For ensuring that all clinical trials conducted in the Community are subject to the same criteria for the approval and supervision of clinical trials, the requirements should be established by a regulation.** All operators within the Community will thus be subject to the same requirements for the approval, administrative treatment and supervision of clinical trials, thereby eliminating, and diverging, redundant and contradicting requirements.

However the choice of a country not to implement a clinical trial on its territory should be preserved.

KEY ISSUE N°3 TO BE ADDRESSED: REGULATORY FRAMEWORK NOT ALWAYS ADAPTED TO THE PRACTICAL REQUIREMENTS

Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

It might be challenging to generally pre-establish the risk of a clinical trial. While it is clear that there is a high potential risk for a non-authorised product, it becomes more difficult to attribute a level of risk for clinical trials testing new indication of an already authorised product or studies addressing the efficacy or safety of an authorised product in a new or extended population. Some of these studies may involve thousands of people.

Therefore sanofi-aventis considers that caution is necessary before considering a risk-differentiation based approach.

The main issue regarding the insufficient risk-differentiation comes from the lack of differentiation between clinical studies which are interventional on product prescription and other studies (*see response on consultation item n° 6*).

Moreover, should the risk differentiation be implemented, the problem of its evaluation (national, centralised) would need to be addressed (additional step).

Consultation item n°10: Do you agree with this description? Can you give other examples?

The implementation of a single sponsor per multinational clinical trial is not an issue for the industry.

Single sponsorship actually ensures the reliability of the logistics (insurance of patients, quality of therapeutic units and of procedures of data collection, etc). The application for a CTA is usually submitted to local NCA by an applicant duly authorised by the sponsor. The applicant is the contact point for NCA and EC.

It is understandable that unique sponsorship may be a concern for academic studies, which do not have an integrated international network with associated defined responsibilities sharing. One example is the need for a unique safety database for academics.

Consultation item n°11: Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

Among guidelines published by the European Commission in EudraLex Volume 10 Clinical Trials guidelines, two of them are specifically focused on safety reporting:

- Detailed Guidance on the European Database of SUSARS (Eudravigilance- Clinical Trial Module) (ENTR/CT4 revision 1, April 2004)
- Detailed guidance in the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3 revision 2, April 2006)

In addition, specific issues related to safety reporting have been addressed in two different Q&A documents also published in Volume 10 (Chapter II and Chapter V).

It might be useful to have clear SUSARs reporting rules to NCA and Eudravigilance presented in one single document incorporating the clarification recently provided in the Q&A documents.

Both Commission guidelines should be revised and clarified especially concerning the following points:

1) Definition of the SUSAR components
   - *Seriousness criteria*: Harmonisation of "important medical events"
   - *Causality assessment*: Binary response (Yes/No) should be used to avoid endless discussions without scientific interest on the identification of a suspected "reaction"
   - *Expectedness*: according to CIOMS III/V recommendations, implementation of a specific section in the Investigator's Brochure dealing with expected adverse reactions.
     - Clarification is needed on the selection of "*the most appropriate SmPC document*" for reference document for assessing expectedness where the IMP has a marketing authorisation in several Member States.
     - Indeed, for a same IMP, the reference document can therefore be different from a trial to another, leading to inconsistency in the expectedness assessment and SUSAR reporting from a country to another country. To avoid this situation we would recommend using systematically the Core Safety Information of the company.

2) Clear rules for SUSARS reporting to NCA and Eudravigilance

   The recommendations for SUSARs reporting provided in the two guidance documents should be clarified and harmonised. The reporting requirements related to different situations concerning the marketing authorisation status of the IMP, the origin of the report (occurring within or outside the concerned clinical trial, within another clinical trial or outside a clinical trial), the nature of the sponsor (MAH or not) are addressed in both guidelines.

   The deletion of wording such as "*whilst the tables seek to address the common scenarios, concerning SUSAR reporting to Eudravigilance in relation to these, it is not intended to substitute for the applicable legislative requirements and guidelines rules*" would help for consistency in the NCA requirements.

3) Clear rules for safety reporting to EC and Investigators

   Section 5.1.6.5 "How to inform the Ethics committee" of the detailed guidance in the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (ENTR/CT3 revision 2, April 2006) should be revised.

   - *Ethical Committees*: In order to facilitate acceptance by all NCAs of Member States of SUSARs periodic reporting to ECs (including a concise safety summary), we would suggest to delete the following sentence: "*In accordance with national legislation Member States may provide that the concerned Ethics Committee only receive expedited individual reports of SUSARs that occurred in subjects who have been recruited in the concerned trial in that Member State*".

   - *Investigators*: Clarification of section 5.3 of this guidance providing recommendation for informing investigators is needed. We would suggest aligning this information with safety reporting to Ethical Committees.

4) Clear rules for the assessment of expectedness are needed

Consultation item n°12: In what areas would an amendment of the Clinical Trial Directive be required in order to address this issue? If this was addressed, can the impacts be described and quantified?

The main area is the reporting of SUSARS. An amendment to the Clinical Trial Directive Article 17 (3)(a) would be required to address that **Competent Authorities should not report SUSARS to EVCTM to avoid duplication and over-reporting**.

Consultation item n°13: Would you agree to this option and if so what would be the impact?

Investigator sponsored clinical trials are clinical trials that are initiated by academic researchers and are aimed at acquiring novel scientific and medical knowledge and evidence to improve patient care.

Investigator sponsored clinical trials issues can not be discussed in isolation from the wider frame of Clinical Trials Directive. Sanofi-aventis believes that the Clinical Trials Directive 2001/20/EC ensures good protection of patients and offers an adequate framework for the conduct of clinical trials. The nature/stringency of the requirements and obligations should not be driven by the status/identity of the sponsor.

Indeed a very positive outcome of the Directive has been the homogeneity of (GCP) standards across phase1- phase 4.

As far as authorised products are concerned, close collaboration with the Marketing Authorisation Holder is essential from the earlier stages to ensure that investigator sponsored clinical trials can produce reliable results. To this end, ad hoc collaborative set between Academia and the MAH is the only way to reduce potential gaps in investigator sponsored clinical trial implementation. The MAH has to be seen as a partner who can bring a strong know-how regarding the product, and can usefully advice on comprehensive planning, state of the art protocol, robust endpoints and adequate sample size. The MAH should have a view on infrastructures and enabling budget.

Consultation item n°14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

We believe that the Clinical Trials Directive is well adapted to paediatric clinical trials.

The Clinical Trials Directive ensures a good protection of paediatric patients and a consistent implementation of GCP.

However we believe that there is a need to increase the dialogue between the various actors involved in the development of paediatric programs (i.e. EMEA PDCO, CTFG NCAs, ECs).
Today, we encounter some difficulties within the framework of the national CTA process (questions from EC and NCA) to implement some modifications in our paediatric clinical trials that have been requested by the Paediatric Committee of the EMEA (PDCO). Ultimately this may lead us to come back to the PDCO for modifications of our agreed Paediatric Investigation Plans, thus generating extra administrative burden and delay. It is important that an effective interface is made available across the different legislative texts. We suggest the European Paediatric Network (created by Article 44 of Paediatric Regulation that the EMEA is currently building) plays a key facilitating role. More information of the current state of implementation of the European Paediatric Network is awaited.

An optional Community CTA will greatly facilitate the continuity and consistency between initial stakeholder opinions/decisions and the following implementation of paediatric investigational plans.

Consultation item n°15: Should this issue be addressed? What ways have been found in order to reconcile patient's right and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?

We believe that the Clinical Trials Directive is well adapted to emergency situations.

No major issues were met in implementation.

Consultation item n°16: Please comment? Do you have additional information, including quantitative information and data?

Sanofi-aventis considers that an accurate description of the situation is presented.

The reasons for conducting clinical trials in third countries are well described. However, **the notion of third countries might need further clarification**: it refers initially to all countries outside the EU whereas the described issues seem to refer to a subset of third countries such as non-OECD third countries. Insofar as third countries are considered as those with less regulation and control for clinical trials, it would be helpful to have a clear definition of the elements qualifying countries as third countries in this restricted sense.

Sanofi-aventis shares the view of the Commission that there's broad consensus concerning the general principles for the conduct of clinical trials in third countries. In fact, for international clinical trials s**anofi-aventis applies the same standards and requirements for all participating countries and trial sites, regardless of whether or not third countries are involved**. Besides internationally accepted standards such as ICH-GCP and the Declaration of Helsinki, the same set of global SOPs is applied for planning, conducting, monitoring and reporting of clinical trials as well as for safety reporting. Measures of quality assurance including auditing of trials and systems are consistently designed and implemented at a global level.

At the same time it is true that in some countries or regions specific local constraints need to be accommodated. For instance, limited access to medicines may have an impact on subjects' willingness to participate in clinical trials as the only measure to obtain treatment thus leading to questions of potential coercion of trial subjects. Informed consent may also be impacted by cultural factors such as subjects' level of education, illiteracy or family/community influences on the subjects' free decision to participate in a trial. Ethics committees or health authorities may work according to different standards and procedures than those adopted in the ICH regions. Lack of appropriate infrastructure, logistics and technical equipment or facilities may pose additional challenges.

When dealing with these challenges, **it is important to find the right balance of ensuring adherence to global ethical principles and clinical trial standards against the respect for specific local circumstances**. Guidance on how to address and satisfactorily meet such challenges would be helpful.

Consultation item n°17: What other options could be considered, taking into account the legal and practical limitations?

Sanofi-aventis considers that the following three measures should be adopted to address challenges to the proper conduct of clinical trials in third countries.

1) **Additional ethical assessment and oversight:** In case local ethical and regulatory standards would not ensure full adherence to globally accepted requirements, an additional Ethics Committee (IEC/IRB) operating according to ICH-GCP standards should be involved.
2) **Transparency:** Sponsors should transparently describe in the clinical study report how particular local challenges were identified and addressed in order to fulfil global ethical and regulatory standards and to adequately protect patients' rights, safety and well-being.
3) **Exchange of information, knowledge and experiences:** Measures should be implemented to facilitate and promote the sharing of best practices in adequately addressing ethical and practical challenges in the conduct of clinical trials in third countries.