Revision of the 'Clinical Trials Directive' 2001/20/EC

European Commission: Concept Paper submitted for Public consultation

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Sanofi-aventis and sanofi pasteur response

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Sanofi-aventis and sanofi pasteur (hereafter: sanofi) consider that a key objective of the Clinical Trials Directive, the "protection of the health and safety of clinical participants" has been achieved.

Sanofi believes that the revision of the EU regulatory framework for clinical trials is now necessary and should be designed to optimise the exploitation of the knowledge generated during the implementation of Clinical Trials. Having the possibility to access and analyse the information and data generated at each moment during the development of a medicine will allow a better understanding on how the medicinal product is being developed. **Enhancing the integrated-assessment of Clinical Trials** at each moment during **the development of a medicine should be one of the objectives of the revision.**

Consultation item n°1: Single submission (with separate assessment)

Sanofi agrees that a single submission through a single EU portal administered by the European Medicines Agency would greatly reduce the administrative work of sponsors.

Beyond this aspect of single submission, we believe that an additional important objective of the revision of the EU clinical trials framework is **to achieve a true harmonization on the elements** to be provided in the submission. Requirements for local specificities should be kept to a minimal level. While we understand that during the clinical trial application for the Ethics Committee's review it will be mandatory to submit specific local documents, we consider that during the CTA submission for "technico-scientific" regulatory authority's review, the submission of a single application is achievable.

Special considerations should be given on the way to submit "local" documents pertaining to each Member State such as WSI, protocol translation, insurance certificates through this same portal in a specific area only accessible to the requiring Member State.

The concept of a single EU portal will also greatly facilitate the management of all subsequent submissions made during the conduct of the clinical trial.
Also the single EU portal may offer the possibility of using cross-references between several clinical trials with the same investigational medicinal product (IMP). This will enhance the regulatory tracking and follow-up across the clinical development of an IMP (integrated overview)

Consultation item n°2: Separate assessment of submitted information

Sanofi agrees that **allowing only a separate assessment by each Member State for the regulatory authority's review would insufficiently address the current issue of inconsistent evaluations**. Alternative regulatory paths should be made available by the Legislator to allow a regulatory review of Clinical Trials at the EU level.

Protection of patients should stay a common responsibility, dealt with at all levels.

At the same time we believe that for Ethics Committee's review a national assessment should be maintained for addressing the local ethical perspective. Nevertheless, **it is of upmost importance that the respective roles and responsibilities of the Regulatory Authority and the Ethics Committee are clarified in a harmonised way across all the Member States.** The technico-scientific evaluation and quality of IMP should be within the sole responsibility of the relevant Regulatory Authority, while applied ethical considerations and site qualifications should be under the responsibility of the Ethics Committees.

Consultation item n°3: Single submission with subsequent central assessment

With the concept of **single submission** that is described under consultation item n°1, sanofi continues to believe that offering the option of **obtaining a harmonised regulatory evaluation of Clinical Trials at the European level would bring meaningful added value to the patients, by making easier the access to multicenter/multinational CTs in all Member States, to a greater number of clinical centres, thus enhancing the overall knowledge and consistency of evaluation of new medicines in the EU.**

We believe that in order to implement and make achievable a harmonised evaluation of CTs valid in the EU **it is unnecessary to establish a formal centralised committee**. Experience from the recent pilot project (the Voluntary Harmonised Procedure) provided some evidence that a European collaborative approach **based on the existing expert network** at NCA level is implementable.

Based on:

1) The institution of a common portal for a single submission,

that also brings

2) The harmonisation of requirements for submission

and could imply

3) Transparency of the ongoing process vis-à vis of all MS,

the necessary further steps to achieve a Community Approval become realistic and would be:

4) **The appointment *via* a written procedure of a subgroup of MSs who volunteer for the dossier,**

5) A **streamlined 60-day evaluation with an opinion that would be immediately valid for pursuing the national step of Ethical Approval** in the involved countries and

6) The opportunity for all other MSs

a) To accept the technico-scientific evaluation by tacit approval, *or*

b) Sending constructive comments during the 60-day review, *or*

c) Opting-out on the basis of explicit divergent view.

Interestingly, *via* this process the scope of the CT evaluation will become a scientific opinion endorsed at the Community level.

More specifically concerning the three objections to a centralised evaluation, as mentioned in the Concept Paper:

- The ethical, national, and local perspectives can and should be evaluated at the national level;
- The same number of Clinical Trials will be evaluated by the already existing network of National Experts, however streamlined by a common portal, according to harmonised requirements and coordinated by the European Medicines Agency
- The formal involvement of all Member States is actually pivotal in fuelling innovation and creating better exchange and equal opportunity for sharing scientific and medical knowledge across the EU; the centralised approach would be a real opportunity for the participation of regulatory experts and clinical centres for the smaller /younger Member States.
- **Reduced fees can be considered for academic centres**

Development of a pharmaceutical product is a long process during which Clinical Trials play a central role, from first in human studies up to large confirmatory studies.

During the development of a medicinal product, the European Medicines Agency is repeatedly consulted on various aspects (e.g., classification, Orphan designation, Paediatric Investigational Plan, Scientific Advice, etc.). Some consultations are mandatory. All Member States participate to these evaluations. Additionally, for some medicinal products the Marketing Authorisation must be granted *via* the centralised procedure (orphan products, advanced therapy medicinal products, mandatory therapeutic areas like dementia, diabetes or cancer, etc). Consequently, at the end of this process the medicine will be authorised in all Member States, irrespective of the conduct of clinical trials in all the Member States.

We believe that an option to offer the regulatory assessment at the EU level for certain categories of clinical trials (the ones directly related with the assessment of safety and efficacy in the intended target patient population) will provide a more robust evaluation at the time of initiation of clinical trials, a more consistent approach during life-cycle management of Clinical Trials, and ultimately a less fragmented implementation of Clinical Trials and a more consistent regulatory approach in the context of the overall oversight of a medicinal product from development to marketing of a medicine.

Involving all the Member States in the review of scientific information available on a product under development will allow the Member States to develop a comprehensive understanding of the IMP during its development and ultimately at the time of evaluation of application for marketing authorisation a better anticipation of its efficacy profile and safety profile.

This possibility for a regulatory evaluation of clinical trial at the European level should be an option for sponsors, coexisting with a national evaluation of clinical trials applications. **Both systems, centralised and national, should comply with the same standards.** Using the network of national assessors available in each Member State for the European regulatory evaluation of clinical trials will ensure the consistency of the evaluation.

This option will provide benefits:

- at the initiation of a clinical trial (timely and simultaneous initiation of the same clinical trial in several Member States, possibility to extend the clinical trial to other Member States in case of difficulties with recruitment in Member States initially involved, of course provided that a national Ethic committee's opinion is granted in these additional Member States);
- during the management of the Clinical Trial (consistent evaluation of amendments);
- during the overall development of an IMP with equal access to all Member States to the experience gained on the product in terms of CTs.

Consultation item n°4: Single submission with subsequent "coordinated assessment procedure" (CAP) – Catalogue of areas

Sanofi agrees with the proposed catalogue to be considered in clinical trials application.

Consultation item n°5: Single submission with "coordinated assessment procedure" (CAP) – Scope including the aspects under a), and only these aspects

As stated in our response under consultation item n°2, we believe that national assessment should be maintained for addressing the local ethical perspectives. Therefore we consider that **only aspects relating to benefit-risk assessment, quality and labelling of the IMP should be included in a joint/centralised assessment procedure.**

However the general ethic principles on which the Clinical Trial is based in relation to the safety and possible consequences for the individual patient and in terms of public health benefits are based on universal principles and should imply common responsibility, which starts at the level of the Clinical Trial design evaluation.

Sanofi agrees that a coordinated assessment procedure may represent some benefits compared to the existing system. However **a decentralised procedure approach will not adequately address the issue of inconsistencies and divergent approaches in the regulatory evaluation of clinical trials.**

The criteria applied during the evaluation of a clinical trial are not fundamentally different to the criteria applied for the assessment of an application for Marketing Authorisation. Therefore the difficulties encountered sometimes with decentralised procedure (i.e., difficulty to obtain a consensus that triggers a referral to the CHMP) may be extrapolated to potential difficulties that may occur during evaluation of clinical trials.

We believe that offering an option to a direct evaluation at a European level will provide a more efficient streamlining and harmonisation of the process for certain categories of clinical trials.

Consultation item n°6: Single submission with "coordinated assessment procedure" (CAP) – Disagreement with assessment report, 3 approaches, which is preferable

Sanofi does not consider that the proposed coordinated assessment procedure will be the optimal solution to streamline the EU regulatory framework for Clinical Trials.

Nevertheless, should the proposed CAP be retained (with a limited number of MS involved in the evaluation) in that case all "concerned" Member States should endorse the final opinion and be bound to the subsequent authorisation.

In case of lack of consensus, this should be resolved by simple majority. If majority cannot be reached, a referral procedure would be the only way forward. However, the additional duration of such referrals to the Commission or the EMA for a decision at EU level may be of concern.

We truly believe that obtaining a decision directly the EU level will be the most efficient process.

Consultation item n°7: Single submission with "coordinated assessment procedure" (CAP) – Mandatory/optional use, which is preferable.

As stated in our response under consultation item n°3, sanofi-aventis and sanofi pasteur support a central assessment rather than a coordinated assessment procedure. However in both cases in order to allow sufficient flexibility this approach should remain optional. **A national system for regulatory evaluation of a clinical trial could remain, provided that harmonisation is reached on various aspects and truly implemented across all the Member States (e.g., documentation to be submitted, definition of IMP, roles and responsibilities between national competent authorities and Ethics committees).**

Consultation item n°8: Single submission with "coordinated assessment procedure" (CAP) – Tacit approval and timelines

As stated in our response under consultation item n°3, sanofi believes that **tacit approval should not be removed from the legislation**. On the contrary, it should be made a rule, if the CAP is retained, to avoid any additional delay and tentative opt out. Member States should not be able to put in stall the single evaluation once it has been approved by majority. Thus tacit authorisation by Member States should suffice (and only its implementation could be put on stand-by at the level of local/national Ethics Committees opinion),

Sanofi welcomes all initiatives to improve timelines; however trials that would fit into the proposed type A category could be subject to divergent interpretation from Member States: as such this new type A would introduce a new area of uncertainties for sponsors.

Type A trials still have to be evaluated for their methodology and scientific plausibility with respect to the questions they are expected to answer.

Consultation item n°9: Scope regarding 'non-interventional trial'

Sanofi agrees with the preliminary appraisal that rather than limiting the scope of the Clinical Trials Directive (CTD) based on a wider definition of "non-interventional trial**", it would be better to come up with harmonised and proportionate requirements which would apply to different type of studies falling into the scope of the revised CTD. Sufficiently detailed provisions on these topics could be included in Annexes to the basic legal act.**

This would be of great added value if the scope of each appendix (e.g. type of studies concerned) is clearly defined. To ensure harmonisation, clear criteria for classification and then operational implementation should be unambiguously proposed otherwise the heterogeneity of the local provisions may increase while we are seeking harmonisation.

In order to better define "non-interventional trial", to the existing three criteria currently defining a "non-interventional trial" (the medicine is used within the terms of the marketing authorisation, there is "no protocol" and "no additional intervention"), we suggest to add another simultaneous criterion of 'Human subject involvement'. In fact, some studies such as retrospective database studies or electronic medical record review do not involve patients *per se*.

In addition, the criteria of "no protocol" and "no additional intervention" seem not well delineated and inappropriate:
- There may be multiple types of protocols (for example: study design protocol, data collection protocol, treatment protocol, patient care protocol pre-existing at the investigator site, etc...)
- There may be also multiple definitions of intervention (for example: use of IMP, patient randomization, informed consenting, data collection, diagnostic procedures, survey, indirect intervention e.g. physician participation in a trial...)

In addition, "out of scope" projects must be clearly defined too. Examples of "Out of scope" projects could be: Project only studying a disease (i.e.: without IMP), projects with no individual patient/subject data collected (e.g.: meta-analysis); no scientific objective (e.g.: market research); named patient programs taking into account products under development.

Clarification should be sought for project studying a disease but requesting intervention on patients (e.g.: biopsy).

Consultation item n°10: Scope regarding nature of the sponsor ('commercial' or 'academic/non-commercial')

Sanofi believes that it would be more adequate to pursue and define harmonized and proportionate requirements for Clinical Trials. Academic/non commercial sponsors should not be separated from this Clinical Directive.
Investigator sponsored clinical trials issues should not be evaluated in isolation or lighter criteria from the current wider frame of the existing Clinical Trials legislation. 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. In particular regarding requirements for the collection, verification, presentation, analysis and reporting of safety data during clinical trials, no exemption should be allowed to academic/non commercial sponsors.**

Consultation item n°11: More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Sanofi considers that as far as the content of the CT application dossier is concerned, **the risk-adapted rules already in place are adequate: Investigational Medicinal Product Dossier can be simplified when studies are conducted with known medicines or when the IMP was subject to a previous Clinical Trial Authorisation.** The conditions under which a simplified IMPD can be submitted are set out in the *Communication from the Commission - Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)*. The detailed guidance must be enforced in a harmonised and consistent way across all the Member States.

Consultation item n°12: Other key aspects on which more detailed rules are needed

Sanofi fully supports that detailed provisions on safety reporting could be included in Annexes to the basic legal act.

The proposed criteria such as the *"risk to trial subject safety compared to normal clinical practice"*, the "*risk to data reliability and robustness*" and "*International harmonisation work, such as the guidelines of the International Conference on Harmonisation ('ICH')"* should be taken into account to establish important key aspects in the study classification.

- The *"risk to trial subject safety compared to normal clinical practice"* criterion is very interesting and critical as it will characterize studies set up in real life. It should be noted that the notion of risk may be subjective. Clear criteria with concrete examples should be given to avoid any inconsistency on the interpretation.

- The "*risk to data reliability and robustness*" should drive the safety reporting guidance for each type of studies including epidemiology environment. Sanofi-aventis believes that the risk adaptation regarding the rules for safety collection, verification, presentation, analysis and reporting should be proportional to the scientific importance of the safety information for evaluating the specified outcomes of interest.
- "*International harmonisation work, such as the guidelines of the International Conference on Harmonisation ('ICH')"* will ensure a consistency within the 3 ICH regions. Opening to other international guidelines (epidemiological guideline would be of great added value).

Consultation item n°13: Combined approach clarifying the definition of 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products'

Sanofi agrees with the proposed definitions for IMP and auxiliary medicinal product.

With regard to the dossier requirements for auxiliary medicines, we considers that clarifications have been worked under the current framework with the *Guidance on Investigational Medicinal Products (IMPs) and 'non investigational medicinal products' (NIMPs)* included in Volume 10 of the Notice to Applicants. In order to make these requirements consistently implemented across all the Member States, it is worth to consider including these detailed provisions in an annexe to the basis legal act, with update when needed by means of delegated acts.

Consultation item n°14: Two policy options on Insurance/indemnisation

Risk characterisation of a Clinical Trial remains a difficult exercise, and therefore may reduce the impact of the first proposal (removing insurance/indemnisation for low-risks trials). Furthermore the insurance issues for the other trials, not considered as low-risks, will not be solved, unless other measures are taken.

The second proposal (optional indemnisation by Member State : obligation for Member States to provide for an indemnisation of damages incurred during clinical trials performed in their territory, taking into account the national legal system for liability) may not contribute towards settling the lack of harmonization and may not lead to a consistent approach between the different Member States. A lack of transparency will certainly remain, for insurance policy terms and conditions as well as loss history. It could also have a side effect of relocating the trials, not taking into consideration the needs of the study, but the policy terms and conditions available locally.

Sanofi believes the best solution would be to set up a minimum insurance coverage, identical in all Member States, with a limit per patient, per trial, and per year (in the aggregate).
The insurers of each country would be able to adapt the premium taking into account the loss ratio, the local legislation and legal context, and of course the nature of the risks for each trial. As the coverage would be minimum it could be increased according to the needs.

Consultation item n°15: Single sponsor

Sanofi is **in agreement with option n°1 to maintain the concept of a single sponsor**. We also strongly support the approach of **truly harmonising the divergent requirements** amongst Member States. However, we recognise that it may take time to reach such an harmonisation and would recommend to allow some flexibility along the lines of the EU Commission guidance provided in volume 10 of the Rules governing medicinal products in the European Union: "A number of parties may agree, in writing, to form an organisation according to Article 2 of Directive 2001/20/EC and to distribute the sponsors tasks/duties and functions between different person(s) and/or organisation(s). This is done in such a way that

the collective agreement fulfils all the required roles and responsibilities of the sponsor." This would be beneficial for instance in the context of public-private partnerships with multiple stakeholders (such as, e.g., IMI). It should also be possible to exceptionally define in writing the respective functions, tasks and responsibilities if sponsorship is shared between two parties, for instance in the case of joint development with partners. Such guidance should be incorporated directly into the revised text of the Directive.

Consultation item n°16: Emergency clinical trials

Sanofi is in favour of defining such common conditions and requirements for emergency clinical trials for the entire EU across Member States. We propose to ensure that these requirements be aligned and compatible with US regulations on emergency research as per 21CFR §50.24.

Consultation item n°17: Ensuring compliance with Good Clinical Practices in Clinical Trials performed in third countries

Sanofi interprets the proposal to enter into EudraCT information on clinical trials conducted in third countries as far as the results of these clinical trials are included in an application for marketing authorisation as an extension of the already existing legal provision for paediatric clinical trials conducted in third countries which are part of a Paediatric Investigational Plan.

Information on these clinical trials may already have been disclosed in other internationally recognised registries. Therefore it would be important that the information required to be entered into EudraCT is fully aligned with the information disclosed in other internationally recognised registries, in order to avoid duplication of data entry and potential for inconsistency in disclosure of information for the same clinical trial. Also clarification on the timing of entering the information into EudraCT will be important (what? protocol and/or results and when initiation of the clinical trial or submission of the application for MA).

Furthermore, sanofi welcomes further clarification of the expectations for CTA and MAA submissions regarding documentation of standards and requirements for trials performed in third countries. However, we would like to request that such documentation be compatible with current standards such as CTA / CTD guidance and ICH E3 in order to avoid duplication and additional bureaucratic burden.

We also recommend to align such expectations with those of the US requirements for foreign clinical trials as per 21CFR §312.120 in order to avoid potentially divergent requirements.

Finally, we are strongly supporting to pursue further capacity building in third countries where needed.

Consultation item n°18: Figures and data

No particular comment.