EUROPEAN COMMISSION: ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE" 2001/20/EC
PUBLIC CONSULTATION PAPER dated 09/10/2009

COLLECTIVE COMMENTS FROM - F. Hoffmann-La-Roche Ltd., Basel Switzerland –(December 17, 2009)

GENERAL COMMENTS

Publication of this consultation paper is welcomed by Roche and also the level of details captured reflects lot of information which has been raised as concerns by us as well as our local affiliates in the individual EU countries over past two years. Our thorough assessment is based on the experience we have made with large number of trials conducted in the EU countries over past years and the feedback collected from the global company perspective, but also from our affiliate perspectives.

Public Consultation Paper

	Commission position/Question	Roche Comments/Suggestions/Proposed changes/Examples
	1. Introduction -	We appreciate that unintended negative consequences are mentioned. It will be important to have some concrete steps which will be undertaken with responsibilities and timelines.
	2. Clinical trials in the EU -	Overall, this section provides good overview and of the current situation Section 2.2- This provides a good assessment of the specific topics which have led to a disharmonised approach due to local and divergent interpretations of the CTD. Table 1 – This table indicates that number of clinical trials conducted in Europe is lower in 2008 and 2009 compared to 2007. This is also reflected in the number of patients planned as mentioned in table 3. If so, is complexity and /or disharmony of the process one reason for this? We think this could be one important aspect.

		- Is there any information on how many of these are first in Human trials for a new molecular entity? It would be of interest to identify if there are different trends according to therapeutic area (e.g. oncology versus CNS) and also with regards to biologics versus small molecules? It would be interesting to know if there are particularly difficulties (or successes) in a given therapeutic area. - There is no information available on how the health authority and ethics committees keep each other informed in a local set-up. Many experiences were made with discrepant opinions from EC and/or HA in the same country. It will be useful to know current processes in the member states and eventually some procedural guidance on possible local alignment to the members states will be helpful.
Consultation Item No. 1	**Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of Clinical Trials Directive?**	Example from Croatia, in a newly approved and valid local Bylaw on Pharmacovigilance there is an obligation to follow principles of CT Directive in terms of full involvement of drug safety Unit within protocol design, approval of safety parameters and processes for collection, analysis and storage of safety data. This empowers involvement of experienced personnel in all phases of clinical trials. Final result is stronger protection of participants. From a German perspective, there is one improvement with respect to the informed consent form: While Germany had different consent forms based on individual Ethics Committee requests, after the implementation of the EU CTD all sites in Germany have to use the same form with the same wording, which was approved by the lead EC. For Belgium there is an improvement of protection of the patient as ICH GCP has now been implemented via national law, mainly applicable for late phase trials. For early phase studies even it was not yet in the law, trials were performed in compliance with ICH GCP. All CEE countries.- Standard set of core study related documents (components of CTA) required by all EU NCAs in CEE. This ensures that decisions of NCAs

		are based on practically the same data and as such more robust as before EU directive. Clinical Trial requirements were embedded into local law in all CEE EU countries. Regarding the benefits of the implementation of the EU Clinical Trials Directive, stricter timelines for the assessment and approval of CTAs by NCA and EC; GCP is no longer just a recommendation, but a mandatory requirement included in the drug law. There is the need to transpose EU Clinical Trials Directive requirements into local law in order to improve patients protection (no hard data however) as it raised a lot of discussion and training within and across EU MSs so could only result in better understanding of principles and process.
Key Issue 1	**Multiple and Divergent assessments of Clinical –**	In this section achievements as well as shortcomings are mentioned. - **On page 11-** ICREL outcomes are mentioned which indicate that there is no decrease in the CT activity in the EU. But the numbers presented in Table 1 and table 3 do not match with these conclusions. Also, we would question whether comparison with 2003 alone is truly representative. In the year before the Clinical Trials Directive was implemented there was a lot of uncertainty, and many sponsors may have taken unusual approaches in the year before (e.g. moving trials away from the EU – making the number artificially low) or trying to initiate more trials in a particular country year before they were affected by the Clinical Trials Directive (i.e. adding more trials in the EU – making the number artificially high). It may be important to compare to years before, before a definitive conclusion is drawn.
Consultation Item No. 2	**3.1** The issue **Is this an accurate description of the situation? What is your appraisal of the situation?**	**Yes, we agree that situation is well described. See comments below.** - Not only that additional local requirements and multiple divergent assessments is an issue, but different requests are coming at various time points from member states. Thus even simple adjustments needed based on local requests from one country results into amendments to the application

		in other countries where the CTA has been already approved. - It is not just the scope of the assessments of NCA and EC of each member state is different, but even within a same member state NCA and EC bodies do not interact with each other resulting in divergent questions and opinions based on same documents and data. Overall, this result in delay, amendments or eventual withdrawal of the CTA from some member states. Thus, we propose to introduce a certain and appropriate level of interactions between NCA and ECs. - It would be helpful if there could be a clear decision regarding which parts of the CTA the NCA should assess and which parts of the CTA the EC's should assess. This should help to avoid contradictory reviews/questions/opinions. - Page 12, paragraph 3 states that '*it has to be pointed out that there are relatively few clinical trials where the application of the regulatory framework ultimately leads to divergent decisions in different MS'*. We would question the validity of this statement as it is unclear how this has been measured. For example if sponsors withdraw the protocol from the MS concerned because a divergent decision is expected, would this be counted as a divergent decision (i.e. sponsors may prefer not to receive a negative decision on a CTA, but may prefer to withdraw)? Is there any way of capturing withdrawal rates? This should be factored into the statement. Examples: Germany could not participate in multinational trials (2 or 3 cases) because the German NCA required changes to the protocol which were not acceptable to the sponsor. Therefore it is a real risk. An additional perspective should be taken into account with respect to the absence of a clear definition of Competent Authority (CA) in the Clinical Trials Directive and the eventual different implementation of this concept in the single member states (existence of more than one CA for different types of clinical trials in some member states. e.g. Italy, Spain.
Consultation Item	**3.2-** Weaknesses of divergent assessments-	**Yes, we partially agree with the assessment. See comments below.**

No. 3	**Is this an accurate description? Can you quantify the impacts? Are there other examples of consequences?**	- First bullet point in 3.2 – The assessment provided in the text that large sponsors have big departments to manage the complexity is not totally correct. In order to maintain the compliance as well as consistency, the company needs to invest lot of resources to manage administrative needs at different time points for multi-state trials without a real benefit to the patients. In our company, administrative burden as well as scattered approval timelines have resulted in over 200% increase in the workforce (at the corporate and individual member state level). - Second/third bullet in 3.2 - It is also about effectively using the expertise in the member states rather than repetitive assessments. Basically, in the company we make sure that highest standards are applied for safety reasons. However, different level of queries are received at different time points from the member states involved. This results in delayed start of the trials or late change suggestions from countries that need amendments once the trial has already been initiated. - Page 13, paragraph 3, first sentence – A delay to study start is not just an issue, but it delays patient access to potentially life-saving/changing trial medications as late trial start leads to late MAA submissions. - Page 13, paragraph 3, second sentence – '*In order to roll out a clinical trial, based on one protocol, in every Member State planned, the sponsor has to wait – apart from the approval by the EC - for the authorisation from the NCA of each of the Member States individually.'* In principle this is correct. We may not necessarily always wait for NCA/EC approval in all countries before starting to enrol patients. But late changes to the protocols in one country lead to amendments in the countries where trial has started. This leads to lot of administrative burden and sometimes may lead to non uniform trials. - It is important to highlight that the different transposition/local instructions in each MS can cause different local outcomes in the same trial (validations,

		documentation/information required, even evaluation results). **Delay and Cost Increase-** Due to non uniform parallel national procedures for CA and EC approvals with different timelines , actual submission and review time of CTA dossier for EU CEE countries is over 5 months (significantly longer than before EU Clinical Trials Directive). This is despite significant additional headcount was hired to manage CTA submissions between 2005 and 2009. US IND application for a particular trial is approved in 30 days which allows earlier first patient entry in the trials in US. However, large time gap between US and EU centres for a common trials results in either overall delay, or amendments to the protocols after initial approvals or eventually dropping some of the EU countries from the trials. There is surely an important increase of costs due to increased resources in Roche Global departments as well as Roche local affiliates and fee payment of CA and ECs.
Consultation Item No. 4	**3.3 -** Options to address issues about assessments **by NCAs** **Can you give indications/quantifications/examples for impact of each option? Which option is preferable? What practice/legal aspects would need to be considered in further detail?**	**3.3.1-VHP option** - the issue as regards the assessment by NCAs We do not have the direct experience of the VHP yet. For two trials which we attempted to discuss about for VHP were considered too complex for the pilot phase e.g. Roche had a trial related to Genetically Modified Organism (GMO) where uniform guidance as well as experience does not exist. VHP approach would have really helped here to get a common position across different member states. Also the timelines are not shortened over national procedures but with two submission waves in the VHP, in fact the process is longer and national option is still considered as favourable option by the development teams. Limitations of VHP- The VHP is not set up as a 'mutual recognition' or 'work

		sharing' procedure and does not make more efficient use of European resources. National assessments are in fact performed in parallel and subsequently shared between the participating NCAs. Since participation is voluntary, member states are free to opt out at any time and choose not to participate. This uncertainty reduces the predictability and planning for the sponsors. After a successful VHP, the sponsor still has to prepare and submit national CTAs in all concerned member states and has to meet all the so called 'national requirements'. The VHP does not address the fundamental problems linked to a divergent interpretation of the Clinical Trials Directive. As long as these problems remain (ex. different remits of NCAs vs. ECs, definition of IMP, substantial amendments, GMP requirements) no voluntary concept will be able to fully succeed. Reliance on voluntary cooperation of NCAs (VHP) and not all member states are part of this activity. Consolidation of questions at one time via VHP procedure could be an advantage. We support the VHP initiative, but the current process needs stronger collaboration from all member states and shorter timelines. We see this as a interim solution. **3.3.2 -Community-wide streamlining of NCA-authorisation process for clinical trials** Streamlining the procedures **Option a- DP/MRP-like procedure-** better alternative compared to national procedure if the process will be bound by tight timelines and arbitration procedure does not lead to a delay. Process needs to be kept simple with common set of requirements.

		Our opinion is the mutual recognition procedure (MRP) was replaced by the so called decentralised procedure (DP) because the MRP was not working satisfactorily for initial applications. So, why an MRP should be more efficient if applied to Clinical Trial Applications? MRP of DP concept assumes a high degree of harmonisation between all the member states. But this is not the case due to divergent national requirements. For instance, the definition of IMP and substantial amendments would vary according to procedure and to the choice of Reference Member State (RMS). Also remit of the CA and the EC also varies from one member state (and potential RMS) to another. Clinical trials need more flexibility and quick actions compared to MAA. Also for CT the country selection is often secondary to the choice of clinical investigators and availability of patients. New investigator sites/ countries need to be added quickly if patient recruitment is unexpectedly slow. Such flexibility for the sponsor does not fit well with a decentralised concept. **This is not recommended or preferred option for Roche.** **Option b-(CP-like procedure)** - **Preferred option as alternative to the current national procedure**. Such one-stop option will provide consistency in the decisions across the EU market. - This will create a link between Clinical development program and the marketing authorisation and will also link to the centralised scientific advice or paediatric procedures, etc. - Sharing of common submission dossier via perhaps a community system like EudraCT will keep the administrative burden to a minimum. **In addition to the national option with more harmonised requirements, we would like to have an alternative optional**

		centralised procedure with a single CTA dossier submitted centrally, reviewed once and resulting in the granting of a Community clinical trial authorisation - valid throughout the countries of the EEA. - Process can be coordinated and managed centrally e.g. by EMEA which already manages the EudraCT and EudraVigliance CT databases, issues guidelines relating to product development and clinical trials. The different EMEA scientific committees (e.g., SAWG/CHMP, PDCO), coordinates GMP and GCP inspectors groups. - This will provide a link between EMEA scientific advice and community CT authorization which is missing currently. - Moreover, an electronic-CTA format and structure, which should be based on the e-CTD specification, should be defined and implemented within this new pathway. Roche believe that a centralised CTA review process with a single Community approval valid for EEA countries would be the logical next step in the legislation. This could exist as an optional procedure, much the same as the centralised procedure was at the outset. The centralised approach would be especially appropriate for not-authorised medicinal products in development (phase I-III) with limited information on the safety profile of the product. This will be in line with the Commission's and EMEA's initiative towards a risk-based approach assessment of medicinal products. For multi-national clinical trials, Roche suggests that the sponsor should be given the choice between the current national systems or alternatively the submission of a single standardised CTA to a central European body, such as EMEA. This body should be empowered to manage and drive the procedure to grant a single Community approval valid for the whole EEA. Scientific assessment of CTAs which can be done either centrally through a dedicated Committee at the EMEA or by delegation to units of competence in a designated MS acting as the Assessor. The evaluation by ECs can be performed

		in parallel in the concerned MSs. A Community decision (approval or rejection) should be granted within 60 days. A clinical trial in an EEA country can be initiated once Community approval and the positive EC opinion from the concerned country are available. The Community and all EC approvals should be published in EudraCT database and concerned competent authorities be notified. EMEA can coordinate the assessment of all post approval activities such as SUSAR reporting, substantial amendments, and the annual safety report (ASR) via the Centralised Committee or the Assessor. A centralized review and approval process of multi-national clinical trials is the only system that allows for substantial reduction of administrative burden and cost both to the authorities and to the sponsors while ensuring highest protection of patients' safety. Resolving the current complications in the initiation of multi-national clinical trials in Europe can facilitate competitiveness of the European research area compared to the US (one-shot submission and 30 days review period) and the emerging countries (India, China, Russia, and Latin-South America). This will be preferred route for our company for multi-state global trials during Phase II, Phase III development stage. Working in this direction will be essential for the company to manage and maintain our clinical development for innovative drugs and more effective EU/global process. Especially for biological compounds and with use of biomarkers etc. this will be important to make use of the best experts available in the community. **3.2.2.2 Scope for streamlining** - CP Process options proposed above should be optional . We think that for the trials involving only 1-2 countries , national approach will be used more compared to community approach for the multi-state trials.

Consultation Item No. 5	**3.4-** Options to address the issue as regards the assessment **by Ethics Committees** **Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical or legal aspects would need to be considered in further detail?**	**We think that all above options are complementary as far as Ethics committees are concerned**. Following all three options will lead to overall alignment in the assessments at the EU level between Ethics Committees across different member states, but also betweens EC's and NCA's. **3.4.1 One-stop shop** for submission of assessment dossier (one submission per country) – If possible this could be the best option to get consistent feedback. Also there is a need for sharing of information by such EC with either a national authority or eventually a community regulatory body perhaps via common database to avoid conflicting positions or at least some process to address if there is conflicting position on protocol or patient safety will be useful. **3.4.2- Strengthening networks** of national Ethics Committees involved in multinational clinical trials (collaboration)- This will also important for consistent standards and resolving conflicting positions on points such as need for DSMB or submission of ad interim data, etc. for seamless design trials or exchange of best practices. In many EU countries there is no national EC but local/ regional ECs that can play role of the Central EC and issue opinion that is binding for all sites in this MS in a particular study. In many cases other local/ regional EC will still be involved in the ethical review despite single opinion procedure used. This is why there are many IRBs/IEC in Europe and why the process is rather complex. It would help not only "logistics", but especially the quality of ethical review if in all MS there are true National EC entitled to evaluate multi-site clinical trials. In Germany preference to have only 1 national EC which is not the case now. **3.4.3 Clarifying the respective scope of assessment of NCA and Ethics Committees** (legal clarity of their respective scope, same in all countries) will be helpful as both receive common documents although not all documents and

		sometimes divergent opinions are obtained at different time points in the community. Some kind of alignment will be also helpful. Furthermore they will not be assessing the same data…e.g. in the Nordic countries. The two bodies are working in parallel, evaluating different aspects of the study. They only have minor overlaps. Splitting the responsibilities for the evaluation of different aspects of the CTA on the CAs and the ECs could allow bypassing the problem of divergent opinions inside one country (e.g. Italy) and could as well give the basis for a centralised evaluation of the CA pertaining documents. Anyway country specific situations should be taken into account - existence of more than one CA and eventual linkages between CAs and ECs due to delegations.
Key Issue 2	**Inconsistent Implementation of the CT directive**	
Consultation Item No. 6	**4.1-** Harmonization Vs Inconsistent implementation of CT directive **Is this an accurate description of the situation? Can you give other examples?**	**Yes, we think that the assessment about inconsistent implementation of the CT directive is accurate.** **4.1.1 Substantial amendments** (21,000 reported/year to NCAs) – Different approval timelines and feedback in multi state trials result in increased number of amendments. Community assessment will reduce the need for changes/amendments drastically. The observation that sponsors consider most of the changes as being substantial could be explained by the extensive list provided as Attachment 5 to the "Detailed guidance on the request for authorisation…, notification of substantial amendments…". According to that list of headings, nearly each change has to be considered substantial. We have also situations where only one country out of perhaps 5-6 who are involved in the clinical trial consider as a particular amendment substantial while others consider is as non substantial. e.g. the German NCA considers an updated IB a substantial amendment even if there is no change in the benefit:

		risk assessment. Substantial amendment should only be submitted to the body who has to assess it (either EC or the HA). **4.1.2 Reporting of SUSARs** (average 5,700/NCA/year) Streamlined common procedure with same information accessible to all will help. Full and consistent implementation of CT Directive would ensure unique reporting processes. With this, different interpretations from the member states could have been avoided. It seems that with respect to SUSAR reporting to ECs/ Investigators / NCAs EU CTD failed to result in harmonization and especially in increasing patient's protection. SUSAR reporting rules in EU MSs are very divergent (from very stringent in terms of what and when to report to more liberal e.g. only Six Monthly Reports). With regards to EC and Investigators it seems that they are not ready to "digest " all the information sent to them in the most conservative scenario (all SUSARs per product as expedited). It would be also important to harmonize SUSAR reporting requirements with other countries worldwide, so that Investigators/ ECs worldwide receive the same information. **4.1.3 Scope of the Clinical Trials Directive** (issue of borderline trial interventional/non-interventional) Discrepancies on the classification of IMPs and non IMPs between Member States in the interpretation of what could be considered as an IMP and non IMPs. This leads to a situation whereby the company needs to plan the clinical trial supply and reporting in a different way for different countries for the same trial. Labelling: different requirements about the information to be included on the

		label between Member States. This leads the company to design different labels to fulfil the different country requirements. Or even carry out some relabeling activities at country level to include additional stickers with the information required. These activities are always on the critical path. Consideration of a valid request for authorisation by the HA exceed more than 60 days in some countries*. This leads to some delays in the clinical trial commencement. **Referring to normal IMP, not involved medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms.* Some Member States apply differently the paragraph 5 of Art.9 about requiring a written authorisation before commencement of all clinical trials. Most of the NCA do not apply the clinical trial application approval by ''positive silence administrative''. This leads to delays in the commencement of the clinical trial and administrative costs. **Examples of divergence –** - Extension of shelf-life: Our clinical trial applications generally include an overall stability plan & shelf-life extension concept. In principle an approval of the CTA should then already include approval of the stability testing plan. As stated explicitly in the EMEA guideline (CHMP/QWP/185401/2004 final) - no further submission of results should be required by agencies - unless test results are not in coherence with the specifications in the already approved CTA. However, in reality - we get asked by agencies at a later time point to submit a CTA amendment for extension of shelf-life. This inconsistency should be clarified and removed. - There has been a case in which the trial was classified as interventional in some MSs but non-interventional in other.

		- Acceptance of "adaptive" protocol design in the MS. - An additional point to be highlighted concerns the definition of Competent Authority, which is left out with the consequence of the setting up of different concepts in the various Member States. This influences national requirements and approaches for different procedures**. In Italy**, for the majority of clinical trials (phase II, III, IV), the actual counterpart for the evaluation of the applications is represented by the ECs due to the limited role of the local CAs in the evaluation process. On the contrary, the Central CAs AIFA and ISS are very active and focused on both the administrative/*IMP-related* and ethics aspects. - Discrepancies between different Member States exist in the implementation of the Clinical Trials directive and as well in the implementation of the related legislation into national regulations (i.e. the Guideline for the request for authorisation of a clinical trial and amendments…, or the setting of specific national requirements for Insurance policies or for CROs). - In addition, differences that could become critical for the management of international clinical trials could be related to what is considered clinical practice in the specific single country. This can result in different definition of which therapies should be considered IMP; to the same consideration refer the topic about the setting of Non interventional perspective trials (concerning the treatment and the visits/laboratory exams).
Consultation Item No. 7	**4.2 –** Weaknesses due to inconsistent implementation **Is this an accurate description? Can you quantify the impacts? Are there other examples of consequences?**	Yes, this is also our observation based on many trials. - It may not be a real issue of patient protection, but more about having the same level of information at a given time to all the parties involved in the trials. SUSAR reporting to sites where the study is being conducted and all critical decisions regarding the patient are taken can really impact on patients safety (if too much is reported or if not enough is reported). It is very important that safety reporting to Investigators and Ethics Committees in EU is truly

		harmonized and optimized. Increased costs- . It is correct that administrative costs to manage compliance have gone up without really any added value in view of the patients safety. This is not just the problem of academic/non commercial sponsors. For our company the costs have gone up by over 200% after implementation of the Clinical Trials Directive without real added value to the patients safety. If more than one body acts as CA/EC in one Member State for the evaluation of the application, multiple payments of fees can be requested (e.g. in Italy) with a result of not aligned costs for the administrative management across Europe. Different country research participation. Countries with additional requirements, longer approval times are generally dropped out from the planned clinical trials if their involvement impacts timelines for completion, etc.
Consultation Item No. 8	**4.3-** Impact of options and preferences **Can you give indications/quantifications/examples of 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?**	4.3.1- Reviewing the Clinical Trials Directive with a view to clarifying provisions, where necessary ……. It would be a benefit if regulations would allow sponsors to send the ASR only to the NCA, and to provide the EC with an annual trial status report (as mentioned in ICH GCP 4.10.1). While the ASR is drug-specific, the annual trial status report would provide the EC with trial specific information, which would allow for continuous review of trial activities. Substantial amendment should only be submitted to the body who has to assess it (or the EC or the HA). 4.3.2- Adopting the text of the Clinical Trials Directive in the form of a Regulation (an overruling, detailed and binding piece of legislation……. This could help in get the local NCAs follow the EU Directive instructions more closely and therefore in a common way by all MSs. • Examples for the impact on each option:

		- SUSARs: avoid duplicate work and speed up the assessment of the safety issues. - ASR assessment on the part of the NCA (and EC): more safety control, but if approval on ASR would be also required this leads to more administrative costs. - The regime for notifying substantial amendments to the NCA/EC if the respective body had not been involved in the assessment of the aspect amended: speed up the amendments implementation. • Practical/legal aspects would need to be considered in further detail: - Harmonisation of the timelines for the HA and EC approval across Europe. - Harmonisation if possible between countries about the documentation required: e.g. no protocol translation into local language required. - Specific requirements when clinical trials on minors. Most of the times the divergent applications are really a consequence of their concrete application of the laws at national level. Normally the national laws do not contradict the Clinical Trials Directive, but Member States normally have local guidances which include the specific requirements that create the divergent applications and assessments e.g. reporting SUSARs to a single Community database which would be regularly evaluated by highly educated group of independent experts. Mandatory follow up of the legislation instead of a directive that should be transposed, should help to standardize requirements and avoid the request of additional requirements or documentation for some MS that increase the burden and prevents for a common approach. EC should also comply with this regulation fully in order to streamline the process. Which option is preferable for improving the situation? Revising the Clinical Trials Directive could be effective in improving the

		situation if the Directive will include a provision that prevents the member states from issuing conflicting national guidance on clinical trials other than on national procedural advice.
Key Issue no. 3	**Regulatory framework not always adapted to the practical requirements**	
Consultation Item No. 9	**5.2.1 –**Insufficient risk differentiation **Can you give examples of an insufficient risk-differentiation? How should this be addressed**?	Harmonization of the risk based on approach across all EU countries is needed. Thus for same type of trial supported by certain data set, the risks could not be different for patients in different countries.
Consultation Item No. 10	**5.2.2-** Requirements not adapted to the practical circumstances **Do you agree with this description? Can you give other examples?**	We agree with the description.
	5.3 Weaknesses	One should not make the assumption that academic sponsors can be treated differently. Industry often makes use of investigator led studies. If they conduct the trial to a different standard such trials can not be used in the marketing authorization applications in the EU, US and ROW.
Consultation Item No. 11	**5.4-** Comments on existing guidelines and possible updates **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 the problem?**	If the Clinical Trials Directive would have been implemented uniformly in all EU member states this would have significantly reduced administrative burden by eliminating the current level of additional national requirements. **Our position-** Overall, it is not considered possible to harmonize the implementation of the clinical trials directive via the introduction of new/revised implementing guidance documents. A new more detailed directive/regulation would be preferred. Improved EU guidance would only help if the member states agree to be fully committed to harmonization and where national differences are simply not tolerated in relation to data requirements, labeling, ASRs, SUSAR reporting, timelines and requirements for substantial amendments. This would be a critical

		first step towards harmonization of requirements across the EU. Example/areas that require further detailed guidance, or greater implementation detail within a revised Directive, to provide appropriate detail for harmonized member state implementation, are given below: - •IMP scope and NIMP criteria to be sufficiently detailed to eliminate ambiguity - Clinical supply labelling - precise details to outlined to prevent national rules and additional requirements - Format and content of ASRs - Annual Safety Reports to contain periodic line listings of all serious ADRs notified to the sponsor during the year under review, and cumulative summary tabulations of all serious adverse events notified to the sponsor, in accordance with the ICH E2F guideline. - SUSAR reporting practices - SUSARs to be communicated to ethics committees and investigators via periodic line listings, each accompanied by brief summary of the evolving safety profile of the IMP. - Some issues such as insurance needs should still remain in the local remit as this cannot be harmonized, but certain minimum criteria/requirements could be included in the guidance as prerequisite for approval. It would be very useful that the guidelines are revised but also to simplify the process and this also increase the risk as there are confusing and too complex processes. Especially SUSAR reporting and IMP labelling should be made less formalistic. Each study IMP label review by a NCA seems to be unnecessary (rather label should be compliant with defined set of core requirements). We support option of reporting SUSARs to a single Community database which would be regularly evaluated by highly educated group of independent experts. SUSAR reporting, single EC approval (single National EC for clinical trials in a MS). In addition it is important that National CAs do not add their own

		interpretation/ additional layers to EU Clinical Trials Directive as this was what hampered harmonization in some areas.
Consultation Item No. 12	**5.4.2**- A Review of the directive and adaptation to practical necessities **In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue? If this was addressed, can the impacts be described and quantified?**	Areas to amend the CT Directive: Text of the Directive current guidelines have been interpreted differently in the individual member states and additional local requirements still need to be fulfilled. • The requirements for content and format of clinical trial applications. Impact: less administrative cost to adapt to the different applications per country and avoid delays in the clinical trials submissions/approvals. Also to make easier the exchange of information among member states because all have the same information. • Clarify what should be the criteria to consider a protocol as a sub-study or an independent study. • Include the definitions of the following terms local interpretations not aligned with the intentions of the CT directive: - Non investigational medicinal product. Impact: avoid different interpretations of the EC guidance on this respect. - Competent authority - Sub-study • SUSAR reporting; submission of annual safety reports (ASR); • Clarification regarding substantial amendments; • IMP labelling in accordance with Annex 13, excluding national peculiarities • Clarification on who is responsible for evaluation of Informed Consent (CA or EC – again divergent scenarios in Europe).
Consultation Item No. 13	**5.4.3**- Exclusion of clinical trials of academic scope **Would you agree to this option and if so what would be the impact?**	It is important that the quality standards of assessment remains unchanged and the same as for a potential future centralised assessments. The quality of the trial must be sufficient for a potential inclusion in a regulatory submission otherwise patients are exposed to trials without the possibility to benefit from a future regulatory approval. One should not make the assumption that academic sponsors can be treated differently. Industry often makes use of investigator led studies. If they conduct

		the trial to a different standard, then these trials can not be used for MAA submissions. To guarantee best protection to all subjects, the nature/stringency of the requirements and obligations should not be driven by the status/identity of the sponsor, but rather by the nature of the investigation. We do not agree with the proposals for exclusion of 'academic' sponsors from the rules of the CT Directive. However, we do recognise the difficulty in complying with the legislative requirements and this has an impact on the ability to conduct clinical research in the EU. A review of the legislation to identify those provisions of the legislation that cause difficulty for 'academic' sponsors. And if there is no safety impact on participants in the trial simplifying the legislation and applying it to all sponsors. This approach would then remove those elements of the legislation that are problematic for 'academic' sponsors while maintaining the high standards of patient safety and ensuring consistency in application of the EU legislation across all clinical trials' sponsors. In order to guarantee the same level of protection for trial participants so-called academic sponsors should follow the same rules as commercial sponsors when conducting clinical trials.
Key Issue No. 4	**Adaptation to peculiarities in trial participants and trial design**	
Consultation Item No. 14	**6.2-** Promotion of research for paediatric medicines via directive **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**	It is important that when the Paediatric Investigational Plans, including the protocol designs, are approved by the Paediatric committee, individual countries would accept such protocols without any major changes impacting the already approved PIP. If there is divergent position by PDCO and NCA this would lead to unnecessary delays in the conduct of paediatric trials and ultimately a delay in availability of new treatments for children. Currently this types of delays seems difficult to avoid.

	the clinical trial participants?	It is also important that the trials in children is done with the purpose to increase the availability of approved medicinal products, not to increase off-label use in this population. It is therefore critical that clinical trials, also with academic/non-commercial" sponsors, are performed with the purpose to generate data for a future marketing authorization in paediatric use. Otherwise there is a risk of unnecessary" exposure in clinical trials of this vulnerable populations or a repetition of a similar study for registration purpose which is against the principle of avoiding unnecessary trials in children. To promote clinical research for paediatric medicines, safeguarding the participating children, the final launch of the EMEA EU paediatric network would be highly beneficial. Currently this network is still not up and running.
Consultation Item No. 15	**6.2-** Emergency clinical trials **Should this issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?**	Revised EU CTD should provide guidance for the emergency situations when legal representative is not available. e.g. German law is not explicitly referring to emergency clinical trials, it is acceptable to conduct clinical trials in emergency situations where the patient cannot provide consent, and a legal representative is not available to consent on behalf of the patient. However, there is a lot of uncertainty, and a revised EU Clinical Trials Directive should provide guidance for the situation that a legal representative is not available. Belgium has similar situation.. Italy - A specific guidance can be developed foreseeing general protocols in place in the clinical sites to allow emergency trials. The guidance would address specific items to bypass not immediate applicability of the requirements of the Clinical Trials directive. About the ICF, for example, a proposal could be the recovery of general informed consent by the patients at the time of the hospitalization for the registration of data relevant to emergency procedures.
Issue No. 5	**Ensuring Compliance with GCP in clinical trials performed in third**	We can see the rationale to differentiate between non – OECD and OECD countries for the purposes of this consultation document. However, this

	countries	classification may lead to the inaccurate conclusion that non – OECD countries may represent a homogenous group and that solutions to address any potential research issues could be applied in a uniform manner. Indeed we also agree that the “quality” of clinical trials conducted in so-called “third countries” is not intrinsically low or lower that in e.g. OECD countries. We even observe that quality generated in Emerging Countries can be better than in Western Europe and USA, if trials are properly organized and supported by quality experts in well chosen sites with a robust motivation for clinical research. In the attached document, we will present data in order to support this impression. In our opinion, cultural diversity or cultural circumstances, social and economical realities, political/governmental factors and experience/expertise are amongst the factors that can influence the way research is conducted in any given country. This includes influence on ethical aspects related such research. In conclusion, it is understood that socio – economic and cultural issues can influence trial conduct but without any negative impact, on compliance with GCP, being observed. In this context, it should be mentioned that ISO 19011 requires an understanding of auditor’s particular social and cultural characteristics when performing an audit. We observe a high level of patient protection and the benefits from novel therapies as well as an elevated level of routine care by investigators when conducting audits of clinical research activities in emerging economies. In our experience and due to the motivational level of study staff, the provision of training and ongoing coaching for investigators, study staff and monitors appears to be a key deliverable. We see the capacity building for the conduct of GCP compliant research as a continuous process by which we assertively address resourcing, training and continuing and mentoring support.

		Roche actively supports such capacity building in joint activities with e.g. WHO, Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP) (http://www.fercap-sidcer.org/new_web/doc/ConferencePresentation2008/1124-08Widler.pdf and FERCAP homepage http://www.fercap-sidcer.org/home.asp) , Asia-Pacific Economic Cooperation (http://www.apec.org/) and many others, as mentioned elsewhere in this document. Roche colleagues from our Quality Assurance Organization published two articles in the area of bioethics: L. Hamadian and A.K. Johansen " Reviewing the Ethical Reviewers" GCP J May 2008:8-10 L. Hamadian and A K Johansen "Countering conflicts of interest in Ethical Review" GCP J May 2009:28-29 In situations that pose particularly complex ethical questions for us as a research based manufacturer, we internally have the opportunity to consult the Clinical Research Ethics Advisory Group (CREAG) which is a paned of independent, external advisers that helps Roche to resolve ethics issues related to research in humans (http://www.roche.com/sust-resethissclint.pdf). Thus we do not only actively promote external, but also internal capacity building. Whilst collecting information from a variety of non-OECD countries where we are conducting CTs, we received evidence of a broad band of activities designed to support and ensure the required GCP and Ethical standards. This conclusion is supported by the fact that in some non-EU countries in Europe, we observe cases of voluntary harmonization with EU law pertaining to the conduct of CTs and Pharmacovigilance. In many other non-OECD countries ICH GCP has been transposed to local legislation while supervision of compliance is being verified by local GCP inspections. We observe the conduct of planned and regular training and education sessions - both driven by the Regulatory Agencies or WHO or by “Think Tank” organizations such as the

		EFGCP, ACRP (http://www.acrpnet.org) or a vast number of locally active groups with varying focus – which in part are named elsewhere in the document. The Roche Development Organization has collected feedback from a variety of countries which we hope is useful for the commission in the context of this consultation. We summarize important activities or elements present in the "GCP framework" developed. **N.B.: Please note that Roche will make available to the Commission under separate cover a more detailed document that will provide many of the local, original laws/ guidance documents and related information from a variety of countries Roche conducts research in. Independent sources of information are also mentioned in the document.** We observe the following elements of a GCP framework in non- OECD countries: ***Company Internal:*** • Global and local operation procedures. • The entire study monitoring and co – monitoring framework. • Audits. • Site Training Monitoring visits. • Training and continuing education utilizing a variety of formats of delivery methods and addressing audiences such as Investigators, (co-) sub-investigators, study coordinators, nurses, biochemists, pharmacists and members of IECs/IRBs with focuses on bioethics and ICH GCP. • Information exchange platforms – e.g. investigator – study teams meetings - global or local. • A network of Compliance and Training staff operating with a global and/or local focus and supported by the Quality Assurance Organization and acting e.g. as an information hub or knowledge sharing organization

		(e.g. to avoid reoccurrence of similar audit findings). **Company External (Regulatory Context)** • Inspections of various systems and locations • Globally and locally applicable laws and guidance documents • Conformance statements to be signed by e.g. investigators prior to conducting research • Legal and procedural frameworks for IECs/IRBs to operate under • IRB / IEC accreditation • IRB / IEC registration • Inspection programmes • Local regulations aligned with e.g. the European legislative texts or adopting laws or guidelines from other countries • Regulatory twinning" projects (e.g. France and Serbia) **At the Interface Between Companies and Regulatory Agencies and International Organizations** • Knowledge Exchange Programmes between Health Authorities and Manufacturers • Knowledge Exchange Programmes between international organizations and Manufacturers **Company External (GCP Alliances, Associations, Collaborations and "Think Tanks")** • Wide array of local and global GCP Associations and "Think Tanks" • Patient organizations (playing an increasing role in our experience) • Local Trial Registries • Industry Associations/Organizations and local or regional Trade Organizations

		More Recent or Novel Approaches • Risk Based Approach for the oversight over Clinical Trials (Roche Quality Risk Management) • IRB Risk Assessment tool which is currently implemented in all Roche Pharma Development Operations Latin America countries (details on the document "ASSESSING ETHICS COMMITTEES IN LATIN AMERICA FOR THE OVERVIEW OF CLINICAL TRIALS" to be provided to you under separate cover).