

EUROPABIO RESPONSE TO THE EUROPEAN COMMISSION CONSULTATION ON THE ASSESSMENT OF THE FUNCTIONING OF THE CLINICAL TRIALS DIRECTIVE 2001/20/EC

EuropaBio is the European Association for Bioindustries, bringing together bioscience companies from all fields of research and development, testing, manufacturing and distribution of biotechnology products. It has 74 corporate and 8 associated members, 4 BioRegions and 26 national biotechnology associations representing some 1800 small and medium sized enterprises involved in research

For further information, please contact:

Dr Christiane Abouzeid
Clinical Trials Topic Leader
BioIndustry Association
Email: cabouzeid@bioindustry.org
Tel: +44 20 7565 7199

Julie Kjestrup
Manager, Healthcare Biotech
EuropaBio
Email: j.kjestrup@europabio.org
Tel: +32 2 739 11 78

Executive Summary

EuropaBio welcomes the European Commission initiative to conduct an impact assessment of the application of the Clinical Trials Directive 2001/20/EC with a view to improving the regulatory framework for clinical trials in the EU. We welcome the opportunity to submit these comments in response to the questions posed in the consultation paper and wish to offer our members' suggestions for reform of the Directive.

The Directive was an important first step towards harmonisation of the requirements and processes between EU Member States, and the Directive could provide potential for synergies and time savings. However, these potential benefits have not been realised because of the uneven and inconsistent implementation by EU Member States. There is an increased bureaucracy and proliferation of Member State requirements, and this has resulted in different regulatory standards being applied in granting clinical trial authorisations.

Furthermore there is no supporting evidence that multiple layers of regulatory approvals required by Member States on a national basis would enhance the safety, rights and well-being of patients at a Community level, the very objectives of the Clinical Trials Directive. On the contrary, these administrative burdens undermine public health in the sense that they risk delaying important medicines being investigated in clinical trials and adding extra costs to product development unnecessarily.

EuropaBio believes that the Clinical Trials Directive should be reviewed and revised, and a new Regulation proposed in order to achieve harmonisation and consistency in the approval and conduct of clinical trials in the EU. The Regulation should describe the framework for a centralised assessment process for clinical trial applications that will run in parallel with the national approval process provided by the revised Clinical Trials Directive with the possibility of mutual recognition of national approvals by Member States concerned by the clinical trial. We believe these parallel Community procedures should seek to streamline the approval process for multicentre and multinational clinical trials in more than one Member State. In our view a revision of existing implementing guidelines will not address meaningfully the fundamental issues outlined in our responses below.

EuropaBio has identified the following key areas for improvement:

- The current regulatory and ethics review processes should be streamlined to accelerate the initiation of trials and allow patients faster access to innovative treatments.
- The roles and responsibilities of National Competent Authorities (NCAs) and Ethics Committees (ECs) in the approval process need to be more clearly defined. Appropriate allocation of responsibilities and better cooperation between the NCAs and ECs will increase efficiency

- during the assessment process. It is important to have a true parallel approach to the NCA and EC approval process in Member States.
- A Community-wide authorisation process by the NCAs should be introduced on an optional basis, while retaining the national authorisation procedure.
 - Work sharing between the NCAs during the scientific assessment of CTA applications should be strengthened to improve regulatory consistency and avoid unnecessary duplication.
 - A common clinical trial authorisation dossier and a European one-stop shop for submission of the CTA application are required in order to overcome the administrative burden experienced by sponsors and reduce costs for multinational trials.
 - Data requirements should be harmonised for all EU Member States and proportionate to the protection of the safety and well-being of clinical trial participants. A risk-based approach would ensure that appropriate levels of scrutiny are applied, regardless of the sponsor, while taking account of the extent of knowledge of the mode of action of the product in clinical and non-clinical settings.
 - A pan-European agreement on the scope of the Directive and definitions, in particular what is a non-investigational medicinal product and what changes to a CTA that are not considered to be substantial, as well as the rules for safety reporting and labelling are required for a harmonised approach to regulation of clinical trials.

We would like to stress that those complex administrative requirements, which do not contribute to patient safety and data quality, and unpredictability of the regulatory process impact acutely on SMEs' research and development operations. This is because continued financing of these companies is contingent upon meeting certain regulatory milestones, including clinical trial approvals, and therefore timelines in grant of a clinical trial authorisation are critically important.

The dramatic drop in the number of drug development companies formed in Europe is of major concern. Better regulation is required now, not in a few years' time, in order to ensure a sustainable and viable bioscience industry in Europe that can compete globally.

The removal of unnecessary bureaucracy would benefit companies and patients by increasing the development and access to innovative medicines. This will make Europe a more attractive place for clinical research and a leading region for innovation.

Clinical trials in the EU

**The Clinical Trials Directive: Achievements but also shortcomings
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?**

The Directive was an important first step towards harmonisation of the requirements and processes between EU Member States. Indeed, the spirit of the Directive is now recognised within the Community since its adoption in 2001.

- Harmonisation of the clinical trial process through the authorisation of a clinical trial by the National Competent Authority (NCA) and a single Ethics Committee (EC) opinion at Member State level within defined approval timelines. However, there is a need to further enhance harmonisation.
- Principle of parallel processing of clinical trial applications by the NCA and EC.
- Compliance with Good Clinical Practice (GCP) for the conduct of clinical trials with medicinal products has a positive impact on the quality of clinical trial data.

EuropaBio is not aware of any studies that showed an improved protection because of the Clinical Trials Directive. We note that the time to start a Phase I study with healthy volunteers has been tremendously increased in some EU Member States following the implementation of the Directive, but this did not contribute to any improved protection.

There is no evidence to support that multiple layers of regulatory approvals required by Member States on a national basis would enhance the safety, rights and well-being of patients at a Community level. Administrative burdens undermine Community objectives of protecting public health in the sense that they delay important medicines being investigated in clinical trials and add extra costs to product development unnecessarily. Increased cost in product development may have a material effect on the pricing of innovative medicines.

Key Issue N°1 to be Addressed: Multiple and Divergent Assessments of Clinical Trials

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

Overall, EuropaBio agrees with this description which reflects the current situation.

Individual Member States have imposed different requirements – some of which go beyond those set out in the Directive, others that appear disproportionate to the objective of protecting safety and rights of trial participants – resulting in different regulatory standards being applied by the Member States in the process of granting clinical trial authorisations. Such differences have adversely impacted on the ability of our member companies to carry out multinational clinical trials, especially SMEs which do not have sufficient financial and manpower resources to effectively deal with different national requirements imposed by the Member States. Indeed, divergent assessments may lead to either amending the protocol or not conducting the trial in the Member State requesting the changes, thereby denying patients' access to new treatments and adding unnecessary administrative burden and costs (see above).

EuropaBio recommends:

- Harmonisation of data and document requirements and clinical trial authorisation processes across EU Member States.
- A common CTA dossier for NCA review across the different Member States. This will help reduce the administrative burden experienced by sponsors and thereby reduce costs for multinational trials. Translations in the language of the country where the sponsor wishes to conduct the study should be limited to the protocol synopsis, patient information leaflet and informed consent form.
- A 'Rolling IMP Dossier' to facilitate submission of technical information supporting clinical trials to a single point of assessment through the different development phases of a medicinal product.
- Identifying the roles and responsibilities of NCAs and ECs in the approval process. Appropriate allocation of responsibilities and better cooperation between the NCAs and ECs will increase efficiency during the assessment process and improve timelines for initiation of clinical trials in the EU.
- Facilitating work sharing between the NCAs during the scientific assessment of CTA applications to improve regulatory consistency and avoid unnecessary duplication.
- A pan-European agreement on the definition of an investigational medicinal product (IMP) versus non-investigational medicinal product (NIMP). This should also seek to limit the increasing information requirements on the quality of non-IMPs that in most cases form part of the 'standard of care' medication.

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

Overall, EuropaBio agrees with this description.

The Directive could provide potential for synergies and time savings. However, these potential benefits have not been realised which has led to Europe being seen as a less attractive location for clinical development. Some countries in particular are avoided as the perception is that the requirements in these territories are constantly changing and increasing.

The inconsistent approach by Member States leads to many national requests for additional documentation to be included in the clinical trial application. Attachment 1 of the Commission's detailed guidance for the request for authorisation of a clinical trial (ENTR/F2/BL D (2003) CT1 Revision 2) lists the documents required by Member State for application to the NCA. It is worth noting that some Member States retain a national application form to be completed in the local language in addition to the European Application Form (Annex 1 to the guidance). Where forms have been developed for pan-European use it is anticipated that there is EU-wide acceptance of them in place of national forms; however, this is apparently not the case.

Examples of the lack of harmonisation in document requirements for the approval of clinical trials are provided in **Appendix 1**.

The administrative burden to identify and comply with additional local requirements is significant. Thus international biopharmaceutical companies have put in place databases to record the divergent Member State requirements, which need to be regularly updated by the affiliated companies. Clearly, such task is time consuming and labour intensive which put all companies at a disadvantage, particularly SMEs.

The patchwork of assessment procedures results in greater complexity and bureaucracy for the sponsor in managing multinational clinical trials, i.e. submissions are made to more countries than necessary to provide a back-up plan with countries being withdrawn from a study if the approval process is slower in comparison with other countries. This represents an inefficient use of resources and duplication of efforts not only for biopharmaceutical companies, but also for ECs and NCAs.

This potentially delays the approval of clinical trials in the EU, without adding further in terms of health protection or improving patient safety.

**Options to address the issue as regards the assessment by NCAs
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?**

Overall, EuropaBio welcomed the Voluntary Harmonisation Procedure (VHP) which provides a useful platform for multinational clinical trial applications. This initiative is a step in the right direction towards greater harmonisation among EU Member States. However, member companies felt that the

proposed pilot process did not address the main issues arising from the uneven and inconsistent implementation of the Clinical Trials Directive. The VHP appears to be attempting to harmonise a *process*, which is a laudable and worthwhile ambition, but not necessarily harmonising the *different national requirements and divergent questions* from NCAs in relation to CTA applications.

EuropaBio very much welcomes the potential options discussed in the consultation document for streamlining the NCA authorisation process for clinical trials in the Community, building on experiences with a similar approach in the procedures already in place for marketing authorisation of medicinal products.

We would prefer that the Community-wide authorisation procedures are introduced on an optional basis, while retaining and streamlining the national authorisation procedure. Member companies wish to have flexibility in choosing the most appropriate procedure with the possibility of switching between the different procedures throughout product development.

However, we would not support that any procedure should be restricted in any way to certain types of products or phase trials. The regulatory approval process that is mandated or planned for the IMP to gain a marketing authorisation should not limit the choice of clinical trial assessment procedure.

The decentralised / mutual recognition procedure (see section 3.3.2.1 (a) of the consultation paper) has the potential to provide an alternative approach to the current national procedure with particular reference to first-in-human trials and trials in two or more Member States. In particular, a high level of harmonisation and trust amongst EU Member States would be a pre-requisite to ensure that the process is not too complex and lengthy.

The centralised procedure (see section 3.3.2.1 (b) of the consultation paper) has the potential to simplify the process for gaining authorisation to conduct multinational clinical trials in the EU. Such an authorisation would be valid throughout the Community and the clinical trial could be rolled out across the entire EU without additional follow up authorisations of Member States. A risk-adapted approach is strongly recommended so as to avoid a combination of all Member States requirements which would defeat the objective of streamlining the regulatory process.

Further consideration would need to be given to how the EC review will be performed in the context of the centralised procedure. It is acknowledged that there is a difference in the regulatory assessment procedure in Member States as well as the importance placed on regulatory versus ethics review. Therefore it is important that there is legal clarity on the roles and scope of assessments of both NCAs and ECs across EU Member States, and the scientific assessment is conducted in parallel with the EC assessment with timeframes allowing for a feedback loop in case of major differences between scientific and ethics assessments.

**Options to address the issue as regards the assessment by ECs
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?**

EuropaBio would be in favour of the option outlined in section 3.4.1 of the consultation paper: a one-stop shop for submission of the assessment dossier. It is desirable to have one single point of entry for submission of the request for authorisation of a clinical trial to both NCA and EC in order to reduce the administrative burden of multiple submissions.

It is recommended that the documents submitted in the application dossier reflect the different responsibilities assigned to NCAs and ECs as regards the assessment of a request for a CTA. This demarcation is necessary to avoid unjustified duplication during the approval process.

The ECs responsibilities should focus on ethical issues, ensuring informed consent of trial subjects, safety measures are in place to minimise potential risk exposure, suitability of investigators and adequacy of facilities. The following documents should only be reviewed by the ECs: informed consent form, patient information leaflet, advertisements relating to patient recruitment, investigator CVs and patients insurance.

The protocol, investigator brochure and the application form (Annex 1 to the guidance ENTR/F2/BL D (2003) CT1 Revision 2) would be reviewed by both NCA and EC.

The IMPD with technical information would only be reviewed by the NCAs, which have primary responsibility for assessing the safety of trials, reviewing the data pertaining to the pharmaceutical and non-clinical testing.

While ethical issues clearly fall within the remit of Member States and would remain there, the Commission suggests working towards greater co-operation and co-ordination between national ECs to improve the ethics review process. It would be helpful to provide pan-European training to ECs to ensure consistency in the approach to assessment across Member States.

However, we would need some further clarification as to how the network of national ECs involved in multinational clinical trials would work in practice, given the following statement:

“Concerning ethical issues, Member States could “opt out” as regards the final result of an assessment of a request for authorisation of a clinical trial.”

EuropaBio supports the option to review the Directive to ensure that there is legal clarity on the remit of NCAs and ECs in Member States (see section 3.4.3 of the consultation paper). This would result in a clearer identification of their respective roles and responsibilities in order to avoid duplication in

assessment, thus improving trial start up times. It is important to have a true parallel approach to the NCA and EC approval process in Member States. In addition, the communication between the NCAs and the ECs should be strengthened.

Key Issue N°2 to be Addressed: Inconsistent Implementation of the Clinical Trials Directive

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

Overall, EuropaBio believes this is an accurate description of the situation. Indeed, the three examples set out in the consultation paper are causing our member companies major difficulties. EuropaBio requests:

- Clear and harmonised definition of “non-interventional trials” agreed by all Member States.
- Harmonised application of the definition of “substantial amendment” and clear criteria for notification of a substantial amendment to the concerned authorities, in particular whether approval is required from the NCA and/or EC.
- Harmonised reporting requirements to address the issue of “over-reporting” of SUSARs. The information obtained from SUSAR reporting should be useful and meaningful so that, following analysis, a thorough understanding of the safety profile of the product and procedures used in the trial is available. This concept should take precedence over the need to submit all information to NCAs, ECs, investigators, etc.
- Safety reporting is centralised using the EudraVigilance database to overcome the administrative burden resulting from country-specific requirements.

EuropaBio would like to draw the Commission’s attention to a couple of best practice examples. This concerns the reporting of suspected unexpected serious adverse reactions (SUSARs) in the Netherlands and clinical method development studies in the UK.

The Medicines Evaluation Board allows for waiver of SUSAR reporting to the NCA if the sponsor undertakes to submit such reports through the EMEA EudraVigilance database within the appropriate time frames. This pragmatic approach eliminates duplicate reporting and demonstrates Member State acknowledgement of European systems.

The MHRA suggests that sponsors use the algorithm provided in Volume 10 - Guidance documents applying to clinical trials (Question & Answers) of the rules governing medicinal products in the EU to establish if their study meets the definition of a clinical trial and is therefore covered by the Clinical Trials Directive. Method development studies may sometimes use marketed medicinal products in order to provoke the pharmacological/physiological

response that itself is the focus of the investigation. The MHRA consistently recognises that clinical method development studies, even when a medicinal product is involved, are not in the scope of the Directive and a CTA is not required.

Other examples of inconsistent application of the Clinical Trials Directive include:

Different interpretation of the definition of an investigational medicinal product

Member companies reported that multicentre trials conducted in more than one Member State pose practical difficulties. This is because some Member States may consider products such as challenge agents and concomitant and background treatments as an IMP, while others do not.

We note that the term “NIMP” has not been defined in the Directive. The concept was introduced by the Commission guidance for the request for authorisation of a clinical trial to the competent authorities and expanded in the guidance on IMPs and other medicinal products used in clinical trials.

In addition, the interpretation of IMP raises a potential ethical conflict. This could be viewed as a financial inducement for the sites (and in some cases the patients) to participate in the studies if companies are required to pay for comparator treatments (standard of care) which ought to be covered by the national health services.

The guidance on IMPs is certainly open to interpretation and has not met the purpose of presenting a common understanding across EU Member States on the definition of an IMP. There is a need for pan-European agreement on definitions.

Different interpretation of the Directive as it pertains to the preparation of IMP for dosing and the labelling of the final container (e.g. syringe or infusion bag) prior to administration

In some Member States the labelling of dosing devices such as syringes and infusion bags has been considered as a process that requires a manufacturing authorisation, whereas other Member States accept that such activities can be conducted by professionally trained pharmacists under governance of Good Pharmacy Practices.

Requirement to provide an investigator brochure for Phase IV studies

There is a need to further harmonise the requirement to provide an investigator brochure (IB) for trials with approved products. Some Member States request a full IB for a Phase IV trial although the summary of product characteristics (SmPC) would be sufficient including more detailed information in the protocol.

Developing national guidance regarding substantial amendments

Some Member States have developed their own guidelines which set out examples of amendments and specifying how these should be handled in

their respective territories. For example, France issued in January 2009 a guidance document which addresses the requirements of AFSSAPS: “Notice to Sponsors of Clinical Trials on Medicinal Products, Practical Documents – Examples of substantial and non-substantial amendments to be notified to AFSSAPS.¹ This guidance lists the substantial amendments that “must be notified to AFSSAPS for authorisation or for information”. Likewise a joint guidance regarding notification of subsequent amendments during the conduct of clinical trials in Germany was issued in 2006/07 by the Federal Institute for Drugs and Medical Devices and the Paul Ehrlich Institute.²

Introducing legislation relating to serious breaches of GCP

The UK has led the way in putting in place legislation relating to serious breaches of GCP. The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (Statutory Instrument 2006/1928)³ which implemented in UK legislation the Commission GCP Directive 2005/28/EC introduced a new requirement that sponsors notify the competent authority of serious breaches of good clinical practice or the trial protocol within 7 days of becoming aware of that breach that may affect patient safety and data integrity. Discussions are underway in France relating to legislation akin to the UK’s legal requirement for the notification of serious breaches.

Latvia, Poland and Slovakia require that issues that impact safety of the trial are reported to the regulatory agency, although this is a narrower definition than in the UK legislation as they do not require reporting breaches that impact integrity of data.

Once again, these examples show that Member States have developed their own rules and guidance rather than applying a pan-European interpretation of the provisions of the Directive which aims at harmonising the regulatory framework for clinical trials.

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

EuropaBio does not believe that an inconsistent implementation of the Clinical Trials Directive has led to insufficient patient protection.

¹http://www.afssaps.fr/var/afssaps_site/storage/original/application/c0fe8565d129a748e6ad03f3c8c48df8.pdf

²http://www.bfarm.de/clin_012/nn_1199780/SharedDocs/Bekanntmachungen/EN/drugs/clinTrials/bm-KlinPr-20060810-klinPr-pdf-en,templatelD=raw.property=publicationFile.pdf/bm-KlinPr-20060810-klinPr-pdf-en.pdf

³<http://www.opsi.gov.uk/si/si2006/20061928.htm>

We do agree however that the inconsistent implementation of the clinical trials legislation has had a significant impact on sponsors in managing safety information. The different reporting requirements will inevitably lead to duplication in efforts and we do not believe that this is consistent with the better regulation principles.

Moreover, ECs are distracted from identifying any potential risks because of the overwhelming reporting of 'routine' SUSARs. This is a major concern to those ECs which do not have sufficient resources to review the SUSAR information they receive.

Options to address this issue - 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?

EuropaBio believes that the Directive should be reviewed and a new Regulation proposed. This would provide the right legal framework for the approval and conduct of clinical trials in the EU. Both legal instruments – the Directive and the Regulation – should be mirror image to each other.

With regards to the introduction of the Community-wide authorisation procedures for clinical trials, a Regulation conferring the European Medicines Agency the power to issue a decision that is binding in its entirety on all Member States should be considered.

The Directive should be amended with a view to clarifying the provisions which are open to misinterpretation and misapplication of the law by the Member States. Many of the weaknesses identified with the current clinical trials legislation and outlined in the Commission consultation paper could be addressed by ensuring greater clarity within the existing Directive coupled with willingness of the NCAs to cooperate, adopt and adhere to common practices.

Key Issue N°3 to be Addressed: Regulatory Framework Not Always Adapted to the Practical Requirements

Requirements not always risk-commensurate - Consultation item n°9: Can you give examples for an insufficient risk-differentiation? How should this be addressed?

EuropaBio believes that data requirements should be proportionate to the protection of the safety and well-being of clinical trial participants. We support a risk-based approach to regulation of clinical trials, taking account of the extent of knowledge of the mode of action of the product in clinical and non-clinical settings. This would reduce workload and costs considerably.

It should be emphasised that the application of such risk-based approach would need to be consistent and in accordance with defined criteria, and the stage of product development. It is also important to recognise that the sponsor could not be asked to provide a clinical trial application for getting approval of a Phase I study, as if it is an application for marketing authorisation. Such a request is wholly unreasonable, and fails to appreciate that product development is an incremental process. We cannot see how a detailed quality section of the IMPD for these early studies adds to patients' safety. The preparation of the IMPD, in particular for biologics, is time and cost consuming and does not add further to the protection of trial participants. We are not aware that the risk to patients notably decreased since the Directive entered into force in 2004.

Requirements not always adapted to the practical circumstances - Consultation item n°10: Do you agree with this description? Can you give other examples?

The concept of single sponsor works well for our member companies. EuropaBio believes that the difficulties experienced by certain sponsors in the academic sector resulted from issues related to insurance and funding of clinical trials.

In addition, Member States have differing interpretation of the role and responsibilities of the EU legal representative for a sponsor based outside the EU. A consistent interpretation and application of Community law would reduce workload.

Review of existing implementing guidelines - 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?

In the short term, a revision of guidelines would be useful but this will not address the fundamental issues arising from the uneven and inconsistent implementation of the Directive by the Member States.

Whilst Commission guidelines have been developed to assist applicants and competent authorities in interpreting the legal requirements, we have observed that certain Member States choose to depart from the recommendations made in these guidelines or apply their own interpretation of these recommendations.

Listed below are examples where guidance revision could address some of the problems:

- Clear definition of what is a NIMP that is agreed and applied by all Member States.

- An agreed list of changes to CTAs that are not considered to be substantial.

Review of the existing Directive and adaptation of the requirements to practical necessities - Consultation item n°12: 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?

Amendment of the Directive is required to ensure greater clarity, certainty and predictability of regulatory requirements for the approval and conduct of clinical trials. This would address definitions, content of clinical trial applications, roles and responsibilities of NCAs and ECs, and help streamline review processes with clear approval timelines as well as harmonise rules for safety reporting (SUSARS and Annual Safety Reports) and IMP labelling and definition of NIMPs.

The removal of unnecessary bureaucracy would benefit companies and patients by improving the development and access to innovative medicines. This will make Europe become a more competitive environment for clinical research and a leading region for innovation.

**Review of the existing Directive and excluding clinical trials of “academic” sponsors from the scope of the Directive
Consultation item n°13: Would you agree to this option and if so what would be the impact?**

EuropaBio does not agree to this option and cannot support a two-tier system. It is critical that the same set of rules is applied to all academic and commercial sponsors in the interests of patient protection.

Unnecessary administrative procedures, which do not improve patient safety and data quality, could have a damaging effect on innovation and increase costs of clinical development. This would have a direct impact on the life sciences industry, particularly SMEs.

A risk based approach would ensure that appropriate levels of scrutiny are applied, regardless of the sponsor. See response to consultation item n°9.

Key Issue N°4 to be Addressed: Adaptation to Peculiarities in Trial Participants and Trial Design

**Option to address this issue – adapting the Clinical Trials Directive
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?

Paediatric trials do not carry less risk than any other trials. Instead of reducing the regulatory oversight of paediatric trials, consideration should be given to removing non-safety related national specificities and purely bureaucratic hurdles for all trials.

Collaboration with patient organisations concerning paediatric diseases would be helpful to promote clinical research for paediatric medicines.

For studies performed in accordance with a development plan for medicines (the Paediatric Investigation Plan (PIP)), we believe that the binding elements of the PIP as agreed to with the EMEA's Paediatric Committee, which pools the best European paediatric regulatory expertise, should not subsequently be challenged by national assessors and ECs. This has a significant impact on the management of clinical trials requiring more resources and adding unnecessary bureaucracy.

Consultation item n°15: 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?

Given that ten Member States have introduced legislation regarding clinical trials in emergency situations, EuropaBio believes that a standard approach for all EU Member States would be beneficial.

It should be noted that there is some limitation to conducting emergency clinical trials, as some Member States request deletion of personal data from such trials if it was not possible to obtain informed consent from the patient.

There is no connection between GCP and personal data protection rules whereas the Clinical Trials Directive expressly requires all parties concerned to have regard to the privacy rules enshrined in Community law.

We strongly recommend that trial documentation are standardised to promote efficiency and harmonisation in the conduct of emergency clinical trials across Europe, while safeguarding patients rights and protection. This is particularly relevant for informed consent form templates, specifying who can sign the informed consent form when the patient is not able to do so.

Key Issue N°5 to be Addressed: Ensuring Compliance with Good Clinical Practices ("GCP") in Clinical Trials performed in Third Countries

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

EuropaBio would like to highlight that companies have policies and procedures in place to ensure that all clinical trials are conducted to the highest standards of GCP, no matter where the trials are performed. Companies have internal procedures to monitor compliance with GCP and ensure that a rapid response takes place to address any breaches of GCP during those trials.

Many companies have been inspected numerous times by GCP inspectors from EU and other regulatory authorities. Such inspections help to ensure compliance with GCP as well as enforcement of those standards.

It is important to emphasise that trials performed in third countries do not necessarily provide data of lower quality.

Therefore we would like to recommend that the results of GCP inspections of third country trials are published to ensure transparency and to dispel the ill-conceived idea that trials conducted in third countries are of lower quality and exploit the vulnerability of people in developing countries.

In addition EuropaBio would like to point out that the results from trials conducted within the EU and in third countries could be used in support of an application for marketing authorisation of medicinal products. Moreover, applicants are required to declare that the trials were performed in accordance with GCP requirements, thus eliminating the possibility that a sponsor would choose a country outside the EU and not conduct the appropriate quality assurance for GCP adherence.

EuropaBio therefore believes that no further legislative action is needed to address this issue. An express reference to ICH E6 guidance should be made in the revised Community legislation governing GCP. We would support further discussions and continued dialogue with the relevant authorities to ensure concerns about GCP compliance of trials conducted in third countries are fully addressed.

Options to address this issue - Consultation item n°17: What other options could be considered, taking into account the legal and practical limitations?

Our member companies expressed major reservations with the option proposed under section 7.3.6, 2nd “linkage”, of the consultation paper. The imposition of a clock-stop for a GCP inspection during assessment of a CTA application would significantly delay the commencement of trials and make the process less predictable and more expensive, thus a further disincentive to conducting trials in the EU.

Clinical trials are increasingly being conducted in third countries, so many (if not most) CTA applications submitted in the EU are likely to include results from third country trials. As sponsors will use the results of these clinical trials

in support of marketing authorisation applications globally, and as GCP compliance is closely scrutinised during assessment of these applications, it is not in the sponsors' interests to apply standards that are not in accordance with GCP.

EuropaBio believes that inspections should continue to be performed as part of the routine inspection cycle which would be sufficient to check GCP compliance.

Consultation item n°18: What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

From a better regulation perspective the view of our members, especially SMEs, is that there is an urgent need to eliminate unnecessary national requirements and ensure the Directive itself is sufficiently detailed to eliminate major misinterpretation and uneven implementation by Member States. To this end Member States must be encouraged to eliminate administrative requirements and, for those required by local law, to amend local laws where necessary to reduce duplicate or additional requirements that cannot be objectively justified. There is a need for a pan-European supervisory function to oversee the correct implementation of the clinical trials legislation.

We would like to stress that unduly complex administrative requirements imposed by either Community law or national domestic law coupling with a lack of predictability of the regulatory process will have a material adverse impact on SMEs' ability to carry out research and development in a cost-effective and efficient manner given the limited time and resources available. This is because continued financing of these companies is contingent upon meeting certain regulatory milestones, including clinical trial approvals, and timelines in grant of a clinical trial authorisation are critically important.

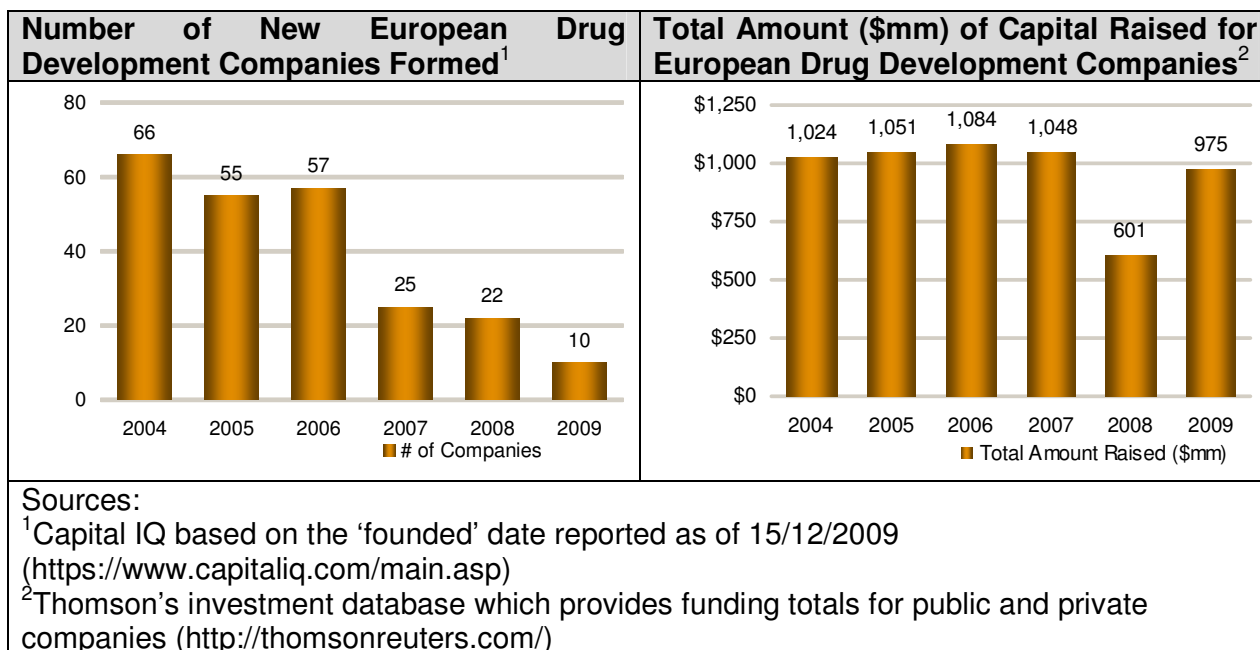
We have presented below some data provided by a member company to illustrate the challenges facing SMEs in developing biologics in the period 2005-2009 in respect of time/costs from discovery to clinical proof of concept. This clearly shows that biologics development is taking longer and costing more.

Value proposition	Time Period (years) From discovery to clinical proof of concept	Direct costs (€ mm)/program
As in 2005	2.5 – 3	10 – 12
As in 2009	3 – 5	15 – 25

Additional research was carried out using information from Capital IQ and Thomson Reuters to determine whether this example is indicative for all emerging companies.

The charts below indicate that there has been a dramatic drop in the number of new European drug development companies formed, yet there has been sustained investment in this period. The drop in formation is a consistent trend, not a temporary aberration caused by the credit crunch (the effect of the latter is seen in the 2008 funding figures). While acknowledging factors besides regulation are pertinent, the financing required per company is clearly increasing. Given the close association between timelines and finance for SMEs it is not unreasonable to deduce that time taken for drug development is increasing and has a detrimental impact on SME formation.

Analysis of the Capital IQ Company Screening Report and Thomson Reuters Investment Analytics Report (2004 - 2009)



The dramatic drop in the number of drug development companies formed in Europe is of major concern. Better regulation is required now, not in a few years' time, in order to ensure a sustainable and viable bioscience industry in Europe that can compete globally.

Appendix 1 - Examples of lack of harmonisation in documentation requirements for authorisation of a clinical trial

Example 1

Protocol A: Requirement for original letters of delegation to a third party to perform the duties of applicant and/or EU legal representative on behalf of a sponsor based outside the EU for a trial with a number of EU centres. This information is already provided in the application form signed by the applicant.

Country	Delegation letter	
	Template	Original
Bulgaria	Local	Yes
Czech	Eastern	Yes
Estonia	Eastern	No
Hungary	Eastern	No
Latvia	Eastern	No
Lithuania	Eastern	No
Poland	Eastern	Yes
Romania	Eastern	Yes
UK⁴	Standard	No

Example 2

Protocol A: Number of non-site specific documents required in the clinical trial authorisation application

Country	Number of non-site specific documents in application
Bulgaria	61
Czech	48
Estonia	41
Hungary	30
Latvia	46
Lithuania	31
Poland	46
Romania	37
UK⁵	13

⁴Included from another study for comparison

⁵Included from another study for comparison