ABPI response to the European Commission Concept Paper on the revision of the Clinical Trials Directive 2001//20/EC

May 2011

Association of the British Pharmaceutical Industry

12 Whitehall, London SW1A 2DY
T: +44 (0)870 890 4333 F: +44 (0)20 7747 1411
www.abpi.org.uk

ABPI response to the European Commission Concept Paper on the revision of the "Clinical Trials Directive" 2001//20/EC

The Association of the British Pharmaceutical Industry (ABPI) represents research-based pharmaceutical companies of all sizes in the UK. The UK pharmaceutical industry is a world leader in the discovery and development of vital new medicines which result in better health for patients here and in other countries, as well as a major contributor to the UK economy.

Our members include the majority of research-based pharmaceutical companies operating in the UK, both large and small. They research, develop, manufacture and supply more than 80 per cent by value of the medicines prescribed through the National Health Service. Our Research Affiliate Members are involved primarily in pharmaceutical research and development, while General Affiliate Members are organisations with an interest in the pharmaceutical industry operating in the UK.

We provide a wide scope of services and support for our members and we represent the views of the pharmaceutical industry in England, Scotland, Wales and Northern Ireland as well as at UK, European and international levels. We maintain close contact with governments, politicians, policy makers, academia and the media and also have extensive links with health managers, patient advocacy groups, training and education bodies, research councils and other professional bodies in the healthcare field.

You can find out more about how the pharmaceutical industry benefits patients and delivers growth for the UK economy in *The Value of Industry* on the ABPI website www.abpi.org.uk

We welcome the opportunity to comment on this European Commission (EC) Concept Paper on revision of the EU Clinical Trials Directive (EU-CTD) 2001/20/EC look forward to continuing to work together, with the Commission to devise processes which will reduce non-value added administrative burden whilst continuing to ensure the safety of patients.

Section 1: Cooperation in assessing and following up applications for clinical trials

1.1. Single submission with separate assessment

Consultation item 1:

We agree with the preliminary appraisal, a single submission would greatly reduce administrative work by sponsors, which currently have to submit varying sets of documents and data individually to each EU Competent Authority (CA). This is similar to the centralised procedure for marketing authorisations.

The key to realising the benefits of this proposal is for there to be common EU clinical trial authorisation (CTA) and Research Ethics Committee (REC) documentation for submission through the 'EU portal', with no additional EU Member State (MS) requirements. This requirement is crucial, regardless of the mechanism for clinical trial applications (centralised or coordinated assessment procedure). The integrated application system (IRAS) in the UK could act as a model for the single portal.

There are some additional points to consider in this item:

- It must facilitate subsequent amendments such as the updating of documentation when additional MS are added to a trial

- Although this will depend on the subsequent procedure, the processing of national fees must be considered. Would this be once via the Portal or direct to the MS at national assessment?

Keeping this this provision optional is important, consistent with other items, it may be more efficient to file nationally for smaller scale trials.

Consultation item 2:

We agree with the preliminary appraisal. Assessment of clinical trial documentation separately per EU MS is wasteful administratively and the current difficulties that have arisen due to independent assessments and divergent interpretation of the legislation will remain, if assessments continue to be performed independently by each MS.

The option to coordinate MS assessment of clinical trial documentation for multi state clinical trials is clearly needed.

1.2. Single submission with subsequent central assessment

Consultation item 3:

We do not agree with the appraisal of this proposal in the Concept Paper.

This provision is of interest to industry for various reasons including the ability to submit a single dossier, centrally resulting in a community CTA, valid throughout the EEA (as per EFPIAs proposal).

It is important for the EU to become more competitive for setting up and performing clinical research in general, in light of increasing competition from non-EU countries. A single EEA CTA would allow faster implementation of a 'second wave' of MS into a multistate trial, which will enhance EU competitiveness in this area.

The central assessment procedure would only be appropriate for larger clinical trials (3 MS or over), which number significantly less than the 1200 per year quoted in the Concept Paper. In any case, it is worth highlighting that any system, centralised or Coordinated Assessment Procedure (CAP), must have the capacity to deal with the large number of clinical trial applications submitted per year in the EU.

The purpose of the central assessment procedure is to streamline the assessment by the CAs of CTAs, not to assess ethical, national or local elements of the trial authorisation process. In section 1.3.1, the Paper outlines the scope of the CAP and the EC recommends the CAP focuses on risk-benefit assessment as well as aspects related to quality of medicines and their labelling. The ABPI agrees with the recommendation for the CAP and believes the central assessment procedure should have the same scope.

Central assessment of CTA should be an optional provision. This mechanism would be best suited to large, late-phase multi-state clinical trials performed by pharmaceutical companies. Increased fees as a result of the multi MS procedure would therefore be appropriate. Smaller clinical trials, including those often performed by academic researchers would be unaffected by this provision and should continue to use simpler (and cheaper) national procedures if appropriate.

The involvement of the EMA should result in better adherence to timelines by the MS. Timelines are key and a workable mechanism must be devised that allows the central assessment procedure to be complete within 60 days, consistent with the CAP timelines. Significant delays to this, caused by a lack of MS consensus for example, would make the procedure unworkable in practice.

1.3. Single submission with a subsequent 'coordinated assessment procedure'

1.3.1. Scope of the CAP

Consultation item 4:

The catalogue provided in Section 1.3.1 of the Paper appears complete. It is important however, that the relative roles of the RECs and CAs are consistently interpreted across the EU, with no variation; (see Item 18), that the process is fast enough to meet the required 60 day timeline and that this process ensures timely provision of national CTA approvals.

In addition, in cases where a first CTA has been approved and the sponsor would like subsequently to extend it to additional MS, the system should allow automatic recognition of the first review by the new MS.

Consultation item 5:

We agree that the scope of the CAP should only be what is captured under bullet a): 'The risk-benefit assessment, as well as aspects related to the quality of the medicines and their labelling'. This should also be the scope of central assessment procedure in section 1.2 (Item 3), as proposed by EFPIA.

1.3.2. Disagreement with the assessment report

Consultation item 6:

We have not chosen a preferred approach. As mentioned previously, timelines are of the utmost importance and whichever mechanism is chosen or devised needs to be efficient so as not to negatively impact the 60 day timeline for the CAP.

Speed is key to maintaining European competitiveness in clinical research and MS opt out is attractive and must be considered for this reason. It is hard to imagine that a trial could be allowed to start in any MS however, if one MS was of the opinion that the trial posed a 'serious risk to public health or safety of the participant'. This makes this provision unworkable in practice in its present form.

Decisions based on MS majority or referred to EMA or the Commission are more robust but could negatively affect timelines. There is a model in the current community practices for the decentralised or mutual recognition procedure which could be considered which is a hybrid between the MS vote and EMA/ Commission decision approaches:

- MS first have to debate and reach a consensus
- In case of disagreement, they should vote
- If a majority is not reached, the matter should be referred to the Commission or EMA

1.3.3. Mandatory/optional use

Consultation item 7:

The CAP should be optional. Consistent with our opinion for the central assessment procedure (see consultation Item 3), we believe that the CAP should be optional. This would allow sponsors to continue to refer to the national procedures laid down in the Directive, if appropriate.

1.3.4. Tacit approval and timelines

Consultation item 8:

The proposal to have a 60 day timeline for the CAP, interpreted as 60 calendar days by all EU MS is supported by the ABPI. It must be noted however, that some EU MS, such as the MHRA, provide national approvals much faster (within 30 days) and the approval timelines for national procedures should not be allowed to slow to 60 days for single MS studies.

The concepts of 'Type A' trials and pre-assessment are both sound but they may add complexity and delay to the trial approval process unless the definition of a Type A trial is clear. Any ambiguity in the definition of a Type A trial will risk internal company disagreements and repeated rounds of discussion between sponsors and regulators. We propose that the sponsor (academic or industry) should perform the pre-assessment of trials and provide the justification to the CA. The agreement or disagreement with the company assessment should be provided swiftly by the CA to the sponsor e.g. within 72 hours.

The concept of 'normal clinical practice' in the Paper should be made as clear as possible. The MHRA have been doing good work on the risk stratification of clinical trials which may be of use in the development of this concept[1].

[1] http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON114358

Section 2: Better adaptation to practical requirements and a more harmonised, risk adapted approach to the procedural aspects of clinical trials

2.1. Limiting the scope of the Clinical Trials Directive

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

Consultation item 9:

We do not agree with this appraisal. It is critical that non-interventional studies stay outside the scope of the Directive. Including them in the Directive will add an additional layer of bureaucracy and act as another barrier to clinical research in the UK and in the EU.

We would support the widening of the definition of a 'non-interventional trial'. In particular, attention must be focused on addressing the phrase 'No additional diagnostic or monitoring procedures are applied' in definition in Article 2c of the Directive. It is this definition that results in many non-interventional studies, performed as part of 'normal clinical practice' falling unnecessarily within the scope of the Directive.

The ABPI supports the harmonisation of requirements for non-interventional studies across the EU but is of the opinion that this work should not be performed as part of the review of Directive 2001/20/EC.

2.1.2. Excluding or not clinical trials by 'academic/non-commercial sponsors' from the scope of the Clinical Trials Directive

Consultation item 10:

ABPI supports this position and agrees with the preliminary appraisal in the Paper. We are of the opinion that the nature/stringency of requirements and obligations should not be driven by the status/identity of a sponsor.

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

Consultation iItem 11:

Consistency across the EU is the most important consideration and the use of guidelines to achieve objectives such as these should be approached with caution as they could open the door to variability.

Content of the clinical trials application dossier

It is essential that all member states are mandated by a Regulation to take the same dossier with no additional National Requirements. This should cover all aspects of the application i.e. scientific, ethical and local. There should be the same requirements for safety reporting, substantial amendments and study closure. This would greatly improve efficiency of clinical trial application work in the EU.

Risk adaptation should be implemented with caution to avoid adding a layer of complexity if sponsors will need to run two different systems (or more) as a result. It was also noted that there already is some risk adaptation in the content of the clinical trials application dossier allowed for in the current Directive, for example, an SmPC can be submitted as the safety

information for a marketed product and most MS will refer to Investigational Medicinal Product Dossiers (IMPD) that have already been assessed. Good work is being done by the MHRA in determining risk based approaches to the management of clinical trials (see consultation Item 8)[2].

Safety reporting

We do not think there should be risk adaptation for safety reporting. Running two different systems would add complexity to an already over-complex system for safety reporting. What we need are the following:

- Streamlined safety reporting rules across the EU, consistent for every MS.

- Expedited safety reporting to Eudravigilance only, with no duplicate reporting to national authorities.

- Safety assessment should sit with the sponsor and competent authorities. There should be no obligation to report expedited or periodic safety reports to RECs (who do not have resource or expertise to deal with these) or investigators (who should receive safety updates via updates to the Investigator Brochure).

- If reporting to RECs and investigators must continue, more detailed rules are needed to clarify what reports are required and the timescales involved for these submissions.

Consultation item 12:

See additional input on the relative roles of RECs and CAs in Item 18.

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

Consultation item 13:

ABPI do not agree with the appraisal. Industry needs a consistent interpretation of what is and isn't an investigational medicinal product (IMP) across the EU, with no variation. We will support any work that clarifies this situation.

The ABPI see no value in generating a regulatory framework for auxiliary medicinal products (AMP)/ non-IMP, we propose that adverse events from AMP should be forwarded to the Marketing Authorisation Holder (MAH) for reporting to the relevant CA via the post-marketing pharmacovigilance system as spontaneous events, if appropriate.

2.4. Insurance/ indemnisation

2.4.1. The issue

2.4.2. Policy options

Consultation item 14:

We are not providing a response to this consultation item.

[2] http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON114358

2.5. Single sponsor

Consultation item 15:

We are of the opinion that Option 1, the concept of a 'single sponsor' should be maintained. This is a complex area across the EU and allowing multiple/ joint sponsorship will make this even more complex. There is also a real risk that this provision will create 'gaps' in responsibility. In addition, a unique contact is desirable, particularly when there is a serious issue.

In addition, the ABPI requests that the European Commission should provide specific guidance on the difference between responsibility and liability with regards to Sponsors.

2.6. Emergency clinical trials

Consultation item 16:

Consistent with the EFPIA position, we agree with the proposals. It is worth noting that there is a UK Statutory Instrument (SI) that relates to Emergency Clinical Trials. (2006 No 2984)[3].

Section 3: Ensuring compliance with Good Clinical Practice in clinical trials performed in third countries

Consultation item 17:

We agree that the principles described in Item 17 could improve GCP compliance in clinical trials performed outside Europe. The possibility of registering clinical trials on other established websites like clintrials.gov should be considered as an alternative to posting on EudraCT however.

Section 4: Figures and data

Consultation item 18: Additional Comments

REC recommendations

There is a clear need to clarify the respective roles of CA and RECs in the assessment process for clinical trials, coupled with a clear delineation of CA and REC roles that is consistently interpreted by every EU MS. This is paramount for reducing administrative burden and streamlining the system. It is worth noting that the Memorandum of Understanding between the MHRA and National Research Ethics Service (NRES) in the UK is a good example of a pragmatic solution that can be implemented ahead of legislative clarification in the revised EU-CTD.

Although not explicitly requested in the Paper, it is important to note that every effort must be made to harmonise the REC assessment process in Europe. Some elements of REC assessment (such as site logistics and recruitment incentives), should remain a national competence to allow local practice, local patient and cultural issues to be addressed but there is a sound argument to say that the ethical standard for Good Clinical Practice in the EU should be assessed centrally. In addition, many improvements to the current situation are possible including:

[3] http://www.legislation.gov.uk/uksi/2006/2984/contents/made

- The use of harmonised EU documentation, with no MS variation.

- Ensuring REC and CA assessments are done in parallel not sequentially and that appropriate timelines (e.g. 60 days for assessment) are set and adhered to.

- Reducing discrepancies in REC opinions, by adequate quality checks.

Additional recommendations

Delays in approvals for substantial amendments are a source of great delay and costs. Including clear timelines for the approval of substantial amendments and ensuring compliance of all MS with these timelines must remain a key aim of the revision of the EU-CTD.

It should be noted, that for various items; e.g. submission of documentation, fee payments, obtaining CTAs etc. it would be prudent to retain the option to use national procedures for smaller scale trials as this may be the most efficient mechanism.

We would like to request the harmonisation and simplification of GMP requirements for clinical trials and for this to be consistently interpreted across the EU.

We welcome the MHRAs excellent example of reduction of administrative burden regarding non-IMPs; these do not require a CTA in the UK and we hope this will remain the case in future.

It is important to note that harmonisation of any process should reflect core requirements required by most MS, not cumulative requirements or alignments to the most stringent MS.

The ABPI would like to thank the European Commission for the opportunity to input into the review of the functioning of the Clinical Trials Directive and hopes that this process of review will remedy the current shortcomings and unintended negative consequences of the Directive, while taking the Global dimension of clinical trials into account and reducing administrative burden.

May 2011