Overview of the EU CTA Regulatory Framework and Future Direction of the EU Clinical Trial Directive

Over the last few years, the European authorities have undertaken substantial new regulatory initiatives regarding the conduct of drug development activities, Clinical Trial Application (CTA) and Marketing Authorisation Application (MAA) submissions.
The EU is a unique economic and political partnership between 27 European countries (Member States-MSs), which have transferred some of their sovereignty – or law-making authority – to the EU “centralised” bodies. Three more countries have applied for EU membership: Croatia, Turkey and the former Yugoslav Republic of Macedonia. In 2007, the Gross Domestic Product (GDP) of the EU was 24700 PPS (Purchasing Power Standard), putting it just behind Japan with a GDP of 27800 PPS and the US at 37300 PPS.

**Member States (MSs) set up EU bodies to run the EU and adopt its common legislation**

The main ones are:
- The European Parliament (representing the people of Europe);
- The Council of the European Union (representing MS national governments);
- The European Commission (representing the common EU interest).

The European Parliament (Europarl or EP) is the directly elected parliamentary institution of the EU. The European Council is the second institution of the EU. It comprises the heads of the state or government of the EU’s Member States (MSs), along with its president and the president of the Commission. The European Commission acts as an executive of the EU. The European Commission is responsible for proposing legislation, implementing decisions, upholding the Union Treaties and the general day-to-day running of the Union. The law of the EU is the unique legal system which operates alongside the laws of MSs of the EU. EU law has direct effect within the legal systems of its MSs, and overrides national law in many areas.

EU Regulation is a legislative act of the EU which requires MSs to achieve a particular result without dictating the means of achieving that result. It can be distinguished from regulations which are self-executing and do not require any implementing measures. Directives normally leave MSs with a certain amount of leeway as to the exact rules to be adopted. Directives can be adopted by means of a variety of legislative procedures depending on their subject matter.

In addition, it is important to keep in mind that national MSs (e.g. France, Italy, Spain, etc.) retain their national laws.

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**The European Medicines Agency**

The European Medicines Agency is a European agency for the evaluation of medicinal products. Previously known as the “EMEA”, it is now called “The Agency”. The Agency was set up in 1995 with funding from EU and the pharmaceutical industry, as well as indirect subsidies from MSs, in an attempt to harmonise (but not replace) the work of existing national medicine regulatory bodies. The Agency operates as an EU decentralised scientific agency (as opposed to a regulatory authority) of the EU and is responsible for the protection and promotion of human and animal health, specifically through the coordination of evaluation and monitoring of centrally authorised products and national referrals, developing technical guidance and providing scientific advice to sponsors.

For products eligible for or requiring central approval, a pharmaceutical company submits an MAA to The Agency. A single evaluation is carried out through the Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP) or Committee on Herbal Medicinal Products (HMPC). If the relevant Committee concludes that quality, safety and efficacy of the medicinal/veterinary/traditional herbal medicinal product is sufficiently proven, it adopts a positive opinion. This is sent to the European Commission for decision and to be transformed into a marketing authorisation valid for the whole of the EU. The Agency’s Committee on Orphan Medicinal Products (COMP) administers the granting of EU orphan drug status. The Agency is also responsible for providing Scientific Advice and Protocol assistance, for assessing the content of Paediatric Investigation...
Features

Plans (PIP) and adopting opinions on them in accordance with Regulation (EC) 1901/2006 via another Agency committee called Paediatric Committee (PDCO), as well as for providing administrative support such as the set up of maintenance of various EU databases and network: EudraCT, EudraVigilance and Eudrapharm databases, etc.

Contrary to the above-mentioned activities (centralised MAAs, EU scientific advice, EU orphan drug status, etc.), Clinical Trial Application (CTA) activities are not handled by The Agency. CTAs are assessed at national level by national Competent Authorities (CAs), who are also responsible for performing CT inspections.

Clinical Trial Regulatory Framework in the EU

The Clinical Trials Directive (Directive 2001/20/EC of 4 April 2001, of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the MSs relating to implementation of Good Clinical Practice (GCP) in the conduct of clinical trials on medicinal products for human use) is an EU Directive which had to be applied by MSs in their national law by 1 May 2004 at the latest. This Directive was created to harmonise CT across the different EU MSs. It is aimed at facilitating the internal market in medicinal products within the EU, while at the same time maintaining an appropriate level of protection for public health. It seeks to simplify and harmonise the administrative provisions governing CTs in the EU, by establishing a clear, transparent procedure.

As this EU CT legislation is a Directive, it is transposed to national law by each MS, meaning that although it aims to harmonise the CT authorisation process, there still remain many national requirements and specificities per MS. Table 1 below summarises a few key points of the Directive.

Table 1

<table>
<thead>
<tr>
<th>Directive 2001/20/ EC-CT Directive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmonisation &amp; transparency in the admin procedure</td>
</tr>
<tr>
<td>Protection of clinical trial subjects - special regard to the treatment of children and incapacitated subjects</td>
</tr>
<tr>
<td>Supportive environment for clinical trials</td>
</tr>
</tbody>
</table>

The major changes introduced by the Directive are summarised in Table 2.

Table 2

<table>
<thead>
<tr>
<th>Major Changes introduced by the CT Directive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear reference to GCP</td>
</tr>
<tr>
<td>One common CTA form for all MS, however additional requirements per MS</td>
</tr>
<tr>
<td>Single Ethics Committee opinion per MS (CEC)</td>
</tr>
<tr>
<td>Requirement for authorisation for Phase I studies</td>
</tr>
<tr>
<td>Sponsor must be based in the EU or have an EU-Legal Representative</td>
</tr>
<tr>
<td>Manufacture of IMPs only at licensed manufacturing sites under GMP conditions</td>
</tr>
<tr>
<td>Specific timetable for CTA review</td>
</tr>
<tr>
<td>CA: 60 for Drugs and Biologics or 90 days (x2) for Advanced Therapy medicinal Products (Cell, Tissue and Gene Therapy) and Genetically Modified Organisms (with/without clock stops depending on the MS)</td>
</tr>
<tr>
<td>EC: opinion to be given within 60 days</td>
</tr>
</tbody>
</table>

EU Clinical Trial Application

To conduct a CT in an EU MS, the sponsor of the CT must obtain, per concerned MS, a positive opinion from the Central Ethics Committee (CEC) and have received no grounds for non-acceptance from the national CA. The application dossier for the authorisation of a CT, to be submitted to the CEC and CA of the MSs, consists of administrative information and the necessary demonstration of quality, safety and efficacy of the Investigational Medicinal Products (IMPs).
Directive 2001/20/EC applies to all IMPs, including the types of products mentioned in Table 3.

Table 3

Directive 2001/20/EC-Appliable to Products
- Chemical entities
- Biotechnology products
- Cell therapy products
- Gene therapy products
- Plasma derived products
- Other extractive products
- Immunological medicinal products (such as: vaccines, allergens, immune sera)
- Herbal medicinal products
- Radiopharmaceutical products
- Homeopathic products

The European Commission published detailed guidance on the application format and documentation to be submitted to request a positive opinion from a CEC or an approval from a CA. These guidances are detailed in Volume 10 of European legislation (Eudralex), and should be followed, taking into account national legislation, in an application to the CA or CEC of the MS in which the trial will take place.

Core documents required for a CTA have been summarised in Table 4 below. The core documents may be assessed by the CA or the CEC or by both.

Table 4

Core documentation for CTA
- EudraCT Number & Application forms (Paper/Electronic)
- Signed Protocol
- Investigator’s Brochure
- IMPD (Investigational Medicinal Product Dossier) for Test Product(s), Placebo and Comparator. Blinding procedure to be detailed if applicable
- Full IMPD
- Quality data
- Non-clinical
- Clinical
- Overall risk and benefit assessment
- Simplified IMPD
- When information about the IMP has been assessed previously as part of a MAA or previous CTA
- When the IMP is a marketed product
- List of Competent Authorities (CA) where CTA has been submitted (Decisions)
- CEC Opinion when available
- PIL/ICF
- Additional MS requirements, e.g. Insurance, Case Report Form (CRF), Contracts

One of the key core documents introduced by the Directive 2001/20/EC is the single CT Application Form to be submitted in all countries to both the CA and CEC. This form is completed using The Agency’s EudraCT system and includes the same information for all countries, with the exception of a few sections (e.g. list of sites to be included).

The EudraCT system must also be used to generate a EudraCT number for the CT. Every CT that is conducted in at least one EU MS must have a EudraCT number. This is the trial’s unique reference number in the EU. This number should be included on the covering page of the protocol and

Table 5: Clinical Trial Application to CA (Vol 10)

<table>
<thead>
<tr>
<th>MS SPECIFIC INFORMATION</th>
<th>AT</th>
<th>BE</th>
<th>DK</th>
<th>FI</th>
<th>FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 General</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 Receipt of confirmation of EudraCT number</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1.2 Covering letter</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1.3 Application form</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1.4 List of Competent Authorities within the Community to which the application has been submitted and details of decision</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1.5 Copy of ethics committee opinion in the MS concerned when available</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1.6 Copy/summary of any scientific advice</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1.7 If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1.8 Will accept application to CA in English</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2 Subject related</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1 Informed consent form</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2.2 Subject information leaflet</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2.3 Arrangements for recruitment of subject</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3 Protocol related</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Protocol with all current amendments</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3.2 Summary of the protocol in the national language</td>
<td>No</td>
<td>B</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3.3 Peer review of trial when available, not compulsory</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3.4 Ethical assessment made by the principal/coordinating investigator</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
be quoted in all communication relating to the trial.

All documents should carry the trial identification (EudraCT number, sponsor’s protocol code number, date and/or version) as well as the version and/or date of the particular document (e.g. when there have only been revisions of the subject information sheet). Under certain circumstances and according to national requirements an abridged application might be sufficient.

CEC and CA applications can be done in parallel or sequentially, depending on the sponsor’s wishes and the national country requirements.

For each CT, there must be an applicant, which can be the sponsor, the sponsor’s EU legal representative, or a third party service provider, such as a Contract Research Organisation (CRO), or, in the case of the CEC application, the local Lead Investigator (local laws apply). The applicant to the CA and the CEC may be the same or different.

Clinical Trial Application to the Competent Authorities

As mentioned previously, the sponsor of a CT must obtain no grounds for non-acceptance from the national CA of the MS in which the trial will take place before commencing the trial.

The application to the CA includes the Investigational Medicinal Product Dossier (IMPD). The IMPD includes summaries of information related to the quality, manufacture and control of the Investigational Medicinal Product (IMP), data from non-clinical studies and from its clinical use. An overall risk-benefit assessment, critical analyses of the non-clinical and clinical data in relation to the potential risks and benefits of the proposed study have to be part of the IMPD. In certain situations, e.g. where the IMP has already been authorised as a medicinal product in one of the EU MSs or where clinical studies with the IMP have already been approved by the concerned MS, a simplified IMPD will be sufficient.

As mentioned earlier, additional MS-specific information is requested from each MS CAs. An example of the CA requirements is summarised in Table 5. This table is not complete, it is only an extract from the complete table provided in Volume 10 and has been provided as an example only.

The review of the CTA carried out by the CA must not exceed 60 days. This period may be shorter depending on national law. If the CA notifies the sponsor of grounds for non-acceptance, the sponsor may on one occasion only amend their request to take into account the grounds given. The approval given by the CAs may be implicit (the trial may commence if the sponsor has received no grounds for non-acceptance within the 60-day assessment period), or explicit (the sponsor must wait for written approval from the CA before commencing the trial), depending on national law.

The review of the CTA carried out by the CA must not exceed 60 days. This period may be shorter depending on national law. If the CA notifies the sponsor of grounds for non-acceptance, the sponsor may on one occasion only amend their request to take into account the grounds given. The approval given by the CAs may be implicit (the trial may commence if the sponsor has received no grounds for non-acceptance within the 60-day assessment period), or explicit (the sponsor must wait for written approval from the CA before commencing the trial), depending on national law.

Clinical Trial Application to the Central Ethics Committee

As mentioned previously, the sponsor of a CT must obtain a positive opinion from the CEC of the MS in which the trial will take place before commencing the trial.

CECs are now regulated by national law Composition, Constitution and Training. According to the Directive the time for response should be 60 days. However, applications to CECs are not completely standardised - each country and each CEC has different requirements and timelines. CECs must be familiar with the provisions of the legislation, data protection, international obligations and rules governing medical research. Members must follow the principles of official accountability and confidentiality. In addition, among other things, the CECs have to consider
1. The study protocol from an ethical point of view
2. Details of indemnity and compensation
3. Details of payments to be made to investigators
4. The adequacy and completeness of the written information to be given to subjects and the procedure for obtaining informed consent.

There are often specific forms required for the CEC submission, and certain forms and/or information are often requested in the local language. Directive 2001/20/EC requests a single CEC opinion per MS. This request has been implemented heterogeneously in the MSs. Some created a single national EC, however in most MSs the local or regional ECs still exist and one is elected as coordinating EC per submission. In such a case the coordinating EC needs to liaise and coordinate the review by the local/regional ECs.

**Clinical Trial Amendments**

Once a CT has been approved by both the CEC and CA, the trial may commence in the concerned MS.

If the sponsor wishes to make an amendment to the CT after its commencement, they must follow the amendment procedure outlined in the Directive 2001/20/EC and the detailed guidance in Volume 10, taking into account national requirements.

In order to reduce the administrative burden for both CT sponsors and regulatory agencies, the Directive 2001/20/EC introduced the notion of substantial and non-substantial amendments. It is the sponsor’s responsibility to assess whether an amendment is substantial or not, based on the guidance provided in Volume 10. Globally speaking, a substantial amendment is any amendment that has a significant impact on the safety of the subjects, the scientific value of the trial, the conduct or management of the trial and/or the quality or safety of any IMP used in the trial. All the amendments should be assessed on a case by case basis by the sponsor whether it is substantial or not.

If an amendment is assessed by the sponsor as non-substantial, it must be recorded in the trial documentation and remain available upon request for inspection at the trial site or sponsor’s premises, as appropriate.

If an amendment is assessed as substantial it must be notified for authorisation or information to the CA or CEC, or both the CA and CEC, depending on the type of amendment and the documents impacted. The responsibilities between the CA and CEC vary according to MS.

The review period for a substantial amendment is 35 days for both CAs and CECs.

**EU Legal Representative**

If the sponsor is based outside the EU, the sponsor must appoint an EU legal representative (EU LR) based within the EU. The EU LR takes on liability for the conduct of the entire study in the EU. However, the sponsor remains responsible for the conduct of the trial.

**Investigational Medicinal Product (IMP)**

The requirements for the authorisation of the manufacturing or importation of IMPs are outlined in Article 13(1) of Directive 2001/20/EC.

All of the IMP manufacturing and importation facilities involved in the CT must be authorised and a copy authorisation is provided in the CTA. If the IMP is manufactured within the EU, and does not have a marketing authorisation in the EU, a GMP compliant manufacturing authorisation must be provided. For IMPs with no marketing authorisation manufactured outside the EU, the sponsor must obtain a statement from the Qualified Person (QP) based in the EU that the manufacturing site is GMP compliant, as well as the GMP status of any active biological substance, and a copy of the EU importing facility’s manufacturing authorisation. These requirements also apply to any comparators or placebos used in the trial.

The sponsor is responsible for the destruction of unused and/or returned IMP. IMP batch records must be kept for at least five years after the completion of the CT, and sufficient samples of the IMP and key packaging components for each finished product must be kept for at least two years.

Re-labelling and over-labelling is very restricted in EU since it falls under GMP requirements, as is reallocation of the IMP from one site to another.
Qualified Person (QP)
An EU QP is required to certify that the batches to be used are complaint with the relevant requirements for their release. The QP ensures batch compliance with GMP, product specification file compliance (testing), product licence compliance with GMP and import/export/record compliance. The QP has a personal liability and is subject to penal sanctions and authorisation withdrawal. When an IMP has been released by the EU QP, no additional import licence is required per country within the EU. However, some countries still have some formalities to follow (for example, France, Poland, Czech Republic). Specific national procedure applies to controlled substances.

Labelling
Labelling requirements in CTs are governed by Annex 13 of Volume 4 (Eudralex) on GMP guidelines. There are some additional national requirements in some countries; for example in Germany the label must include the EudraCT number and the contact details for both the sponsor and the CRO or Investigator. IMP labels must be translated into the national language including specific standard terms, such as "for clinical trial use only", "expiry date" or "keep out of reach of children".

Insurance
CT insurance for the Clinical Trial is mandatory and must be issued according to the national legislation of the concerned MS. Certificates are issued in the national language and are reviewed by the CEC assessing the CTA.

Adverse Event Reporting
Adverse event reporting during CTs is governed by the Directive 2001/20/EC in association with Volume 10 and national requirements.

In the EU, sponsors are required to collect and record all serious adverse events (SAEs). However, expedited reporting to the authorities is only required for suspected unexpected serious adverse reactions (SUSARs). SUSARs must be reported to all CAs and CECs within seven days of occurrence for events that are fatal or life-threatening. For other events, the SUSAR must be reported in fifteen days. SUSARs must also be submitted by the sponsors to The Agency’s EudraVigilance system to be recorded in the EU database. In some countries, waivers or exemptions to report SUSARs to the concerned CA may be obtained on the condition that reporting is carried out to EudraVigilance. Generally speaking, as only reactions are expedited to the CAs and CECs, that is, events related to the concerned IMP, unblinding of the patient’s treatment is almost always necessary.

All serious adverse reactions (SARs) collected during CTs with the concerned IMP are reported to all the CAs and ECs in the form of an Annual Safety Report (ASR). Six-monthly line listings are also required by some CECs. The "annual" date is determined by the date of the first CT authorisation with the IMP in the EU. ASRs must be submitted within 60 days of the data lock point.

Adverse event reporting is carried out per IMP, not per CT, meaning that SUSARs from all countries where a CT with the same IMP is being conducted must be reported (cross-reporting). Likewise, an ASR presenting data collected during all CTs ongoing in the EU with the same IMP is submitted to all MSs in which a CT with the IMP is being conducted.

SUSARs must also be notified to all the investigators participating in the trial, although there is no specific timeline for this.

Alternative Clinical Trial Applications
There are some alternative procedures for CTAs in the EU that can be used depending on the type of product concerned, and the sponsor’s regulatory strategy. Some MSs offer a pre-assessment of the CTA for “high-risk” products or trials (such as first-in-human trials). This can be beneficial to the sponsor so much as it reduces the risk of refusal of the CT. However, there are generally no specific timelines for a pre-assessment, so the sponsor should be prepared for a potentially longer process.

Another procedure that can be used by sponsors is the Voluntary Harmonisation Procedure (VHP), which was set up by the Clinical Trials Facilitation Group (CTFG), and is currently in a pilot phase. The aim of this procedure is to encourage a collaborative review of the CTA by the concerned MS CAs. It is applicable to multinational trials with an IMP without a marketing authorisation in the EU, along with other criteria. The procedure allows eligible sponsors to “pre-submit” their CTA to the
CTFG for review by the national CAs. The CTFGs will issue an opinion on the CT before the official submission to national CAs is carried out. As the national CAs already reviewed the CTA, the official submission process should therefore be very quick, and the outcome in line with the opinion issued by the CTFG.

Finally, Scientific Advice that can be targeted to clinical development is offered by most CAs in the EU. This allows a discussion of draft protocols and clinical development plans before an official submission for review and assessment.

Impact and Future of the Directive 2001/20/EC

The impact of the Directive 2001/20/EC was discussed at a public meeting at “The Agency” in October 2007 and a formal impact assessment of the Directive is currently ongoing (outcome expected summer 2010). Overall, the feedback, based on the result of the ICREL study performed in 2008, is that CTs in the EU have become more difficult and more expensive. Although the Directive has brought improvements and more consistency, it is generally felt that the aim of harmonisation across the EU MSs has not been achieved with the Directive.

There are still many key areas where actions is required, such as the definition of IMP versus non-IMP (NIMP), clarification of substantial amendment versus non-substantial, total harmonisation across EU MSs with a single CTA, clarification on the GMP requirements for IMPs and clarification of the responsibilities between CAs and ECs. There is clearly a need to decrease the administrative burden for CTAs and regulatory maintenance during the course of the CT, especially for multinational CTs. The costs to maintain regulatory intelligence for the 27 MS national legislation, in addition to the regulatory surveillance at EU level is also to be considered.

As for the future of CTAs in the EU, there remain a lot of issues to address and improvements to consider. Should there be a new EU Regulation governing CTs rather than a revised Directive, could revised guidelines be sufficient? Could a single CTA submission be introduced through the EudraCT system? The EU MAA model of a centralised or mutual recognition procedure could be considered for CTAs; the overall aim being to limit the administrative burden of several different submissions to countries that still maintain different requirements. Aside from the notion of a single submission, it also should be considered that more transparency is needed, and fixed timelines for the CAs and CECs scientific assessment (e.g. 30-day deadline for questions from the CTA). A provision for pan-European training for assessors to encourage consistency in their approach should be considered.

Conclusion

Although the 2001/20/EC Directive is not perfect and did not achieve all of its objectives, it has brought a certain harmonisation to CTAs in the EU, and in particular aligned Central and Eastern Europe. Discussions are underway among the EU regulatory agencies and the pharmaceutical industry to further improve the CTA process in the EU.

In the context of overall product development, CTs are critical for the MAA and are key in maintaining communication with CA and the medical and scientific community in the EU. They facilitate efficient development of medicinal products, and support improved access by EU patients to innovative medicines.

Voisin Consulting

Voisin Consulting assists biotechnology, pharmaceutical and medical technology companies in the design and implementation of innovative and global regulatory strategies in order to expedite product development. Products include drugs, biologics, medical devices, combination products, advanced therapy products, as well as borderline products (food supplements and cosmeceuticals). Voisin Consulting collaborates with start-ups and mid-size companies to bring products to the market in the most efficient and cost-effective manner, within an evolving regulatory framework.

References

4. Christine Fretten, Vaughne Miller, The European Union: A guide to terminology procedures and sources, UK House Of Commons Library, International Affairs and Defence Section, (Both the Council of Ministers and the Commission are empowered under the EC Treaty to make laws).