Confidential

TiGenix

DEFINING THE CUTTING EDGE IN REGENERATIVE MEDICINE

Dr. Ch. Siebert
DG Enterprise
EU Commission - Brussels

Leuven, 30 April 2004

Re : TiGenix extra concerns on proposed 'Future European Regulatory Framework for human tissue engineered products' – Stakeholders feedback following Stakeholders' Conference of 16 April 2004.

Dear Dr. Siebert,

Following the meeting of 16 April and the request to submit any other information, questions or concerns to your offices, we would like to take this opportunity to bring 2 other items to your attention.

The first is related to Protection of Intellectual Property / Data Protection in relation to Clinical Trial Autorisation procedures, as it stands now at national level within the EU and the related major (potential) conflicts of interest.

The second is related to certain choices that still need to be made developing the legislation further in relation to allowance of products to the market.

Point 1. The texts now being developed relate to Market Autorisation of TEPs. However, as pointed out before and during the meeting, this process starts already much earlier with asking Clinical Trial Autorisations.

These Autorisations are being processed at National level in the Member states. TiGenix started a multinational, multicenter, prospective, randomised, controlled Phase III clinical trial in 2002. Certain countries had the notification system in place, others already the Authorisation route. The trial will finish recruitment by the summer of 2004. This has been a major undertaking for a small SME that was not even required to undertake clinical trials for its product at that moment, and could have gone to market immediately .

The country – France – with the most advanced system in place of Clinical Trial Autorisation – has not even started ! – although the procedure started 24 months ago and EC approval was obtained 13 months ago.

It is not so much on the timeline that we would like to present this information to you, but rather we would like to present this as a case in point with reference to major conflicts of interest discovered in the 'clinical trial autorisation assessment procedure' because of the lack of transparency, non-declaration of conflict of interest of reviewers that are outside experts and total non- protection of submitted data when a system of untransparant use of experts (non-National Authority employees) is used.

What is the problem ?

In general, the moment when Clinical Trial Autorisation is asked the compound is still 2 to 4 years from potential Market Autorisation.

A review committee, consisting of (entirely) or almost entirely non-regulatory National Authority employees) reviews the data submitted in order to obtain CTA.

The data being asked for (certainly under CTD) is so extensive, that the risk of Intellectual Property coming into the hands of ALL the experts in the review committee is a fact. (The committee easily consists of 20 to 25 people- the dossier is sent all over the country – to Academic institutions).

Because of the particularity of the situation in France, where most of the research AND commercial applications of these TEPs are now being done or are submitted through hospitals/academic institutions, there is a REAL risk that the information from a commercial SME which is submitted in view of Clinical Trial Autorisation (not yet Market Approval) is drained , redirected and absorbed by the academic experts/ institutions performing the review and that at the same time the dossier of the SME submitting is stalled.

The extra adherent risk is that the SME would not even know or would never be in a position to know, because the names of the reviewers are not released, the Conflict of Interests are not declared, the reviewers that have a conflict of interest are not excluded from the review, the minutes of the meetings and the discussions are not shared. The risk than of transferring IP on the one hand and blocking a Clinical Trial Application on the other hand, potentially using the IP information to own benefit of the reviewer and the SME never knowing , because the fact could well not reach 'the visibility limit' is clear and existent .

TiGenix as such is in agreement that expertise should be pooled, however since Clinical Trial Authorisations are still national and no level playing field is created as yet and transparancy is inexistent with regards to CTA review, we plead for a Central oversight as much as possible, creation of transparancy and we would strongly request that ALL present and future procedures are reviewed with 'Good Governance Practices' in mind.

With a situation – for Clinical Trial Approval – as in France, TiGenix is seriously considering withdrawing its dossier and if no better guarantees can be given, it is indeed true as hinted also by other stakeholders present at the conference that SMEs are in no position to further undertake clinical research under the Clinical Trials Directive. TiGenix as such has therefore, taken the step very recently to look at alo development in the US.

The second item we would like to discuss is the 'equitability' of the measures to be undertaken. The balance that will need to be struck between on the one hand making quality, safe and efficacious products available for patients in the EU and the regulatory legislation imposed at a later date.

We would briefly like to highlight our point with a case. In order to do that we have to limit ourselves to the TEP area that we know, being musculo-skeletal repair and to products that are on the market or will be in the near future.

The EU never asked for safety or efficacy of products to be proven uptil now – some countries did not even ask for quality requirements. That has recently changed somewhat on the 'cross-contamination and quality front, but not on safety or efficacy point of view.
In the EU some 20 – 25 products are all in the same therapeutic area, on the market or being developed, for the same type of patient, for the same type of claim. Those on the market have not been asked to proof efficacy. Some 8000 patients have already been treated in the EU.

In the US, proof of quality, safety and efficacy, was introduced in 1997. Only 1 product is on the market. (grandfathered) That manufacturer was asked to provide clinical trial data, received time for that, but when the trial was never done, the FDA ruled that the claim of the manufacturer was downgraded to last line therapy for that type of patient and indication. All future developments needed to be in line with regulators' guidance.

What choices in Europe will be made ? On the one hand we develop legislation where Clinical Trials are necessary for 'cell therapy products' (Clinical Trials Directive), we include Somatic cell therapy products in pharmaceuticals legislation (creating confusion), we include cells and tissues also in the Dir.2002/0128 and manufacturers now on the market just continue to provide products based on minimal criteria and are not really stopped with a request to submit proof of efficacy.

On the other hand large numbers of patients have been treated with no major events reported in the musculo-skeletal area, provided that if there would be events, the community would know.

This is creating 'generic competition' from the outset, which is not really supporting the high-quality and research and innovation environment that one would wish to introduce.

On the other side there seems to be a large number of patients that are quite pleased with the cellular implantation products they received. This calls perhaps for

a balance between pre- and post approval commitments from ALL manufacturers (also tissuebanks, hospitals etc…).

Definitely urgent guidance is needed to cover the interim period until the new TEP legislation is eventually approved, since confusion with Manufacturers (and the legal insecurity resulting from that – also at National Authority level) is high.

We thank you and the Commission for the opportunity to provide comments. Should anything be unclear please do not hesitate to contact us.

Yours sincerely,

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