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PUBLIC CONSULTATION PAPER ON THE REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS

To whom it may concern,

In the 21st century we face unsolved medical problems. Amongst these, some cancers still cost a lot of years of life of the European citizens. One of them is the malignant glioma, which occurs with an incidence of only 3/100000 adults per year, but which causes the highest number of loss of years of life, because of its occurrence at younger age and because of its fatal prognosis.

We also face a lot of opportunities towards new treatment approaches. First of all, there are innovative drug developments. Besides these developments, tissue- and cell-based therapies are under development in many European centres for cancer as well as for other diseases. These products aim to control disease, to establish new equilibriums in the body and/or to restore tissue. Cell-based approaches obviously fall under the regulations for **Advanced Therapy Medicinal Products**. However, if such product falls under the **hospital exemption**, then we come in the scope of Dir 2004/23/EC, being the GTP framework. This framework allows clinical trial material for clinical research. However hospital exemption within this GTP framework excludes clinical research. Both hospital exemption and the GTP framework are regulated by the member states. Moreover, if a cell product is in clinical trial conform the GTP framework, the IMPs require a GMP framework. So it is nowadays not very clear how the directives are interacting with each other.

We, and others, have meanwhile clearly demonstrated the change in prognosis when patients are treated with cell-based therapies. In our case, we use patient-derived mature loaded autologous dendritic cells loaded with autologous tumor lysate to treat patients with malignant glioma. We were able to gain many years of life with good quality of life. Publications are available on our website: www.itpl.be. Our program expanded exponentially, and now patients from 19 neuro-oncology centres within Belgium, and 24 countries outside Belgium are referred to our centre for treatment. This demonstrates the need for such type of solution for the patients. Colleagues send their patients a long distance to obtain ultimate chances. We attempt now to implement our technology in dedicated centres in other countries so that patients get access to the treatment modality more close to home[1]. By networking in the HGG-IMMUNO-Group, we aim to streamline technology and quality control, and to sample the patient data so that experiences are bundled while the treatment is accessible for more patients more close to home. As HGG-IMMUNO-Group, we negotiate with companies to lower the prices for consumables. Hence, there is a win-win-win-win situation: for the patient (high quality innovative treatment close to home), for the science (fast sampling of large data sets), for the companies (connection to large network), and for the community (prices as low as possible).

A lot of cell therapy products are produced in highly specialized medical centres for small numbers of patients, and very often on a 100% personalized basis: one cell product specific for one patient. This means very small productions on a scale per patient. In this situation, the starting material is often very different. In our case, we have two starting materials: a malignant glioma which is obtained from the operation room. The tumor can be located in all possible areas in the brain, the tumor can be resected completely or partially, the tumor can have more or less bleeding/necrosis, the tumor can be derived from a pre-irradiated area in the brain or not, etc. The second incoming product is the leukapheresis product from which we use the monocytes. The monocytes are derived from very ill patients who just got major neurosurgery, who needed in the period before longer or shorter, lower or higher dose of corticosteroids, antibiotics, parenteral fluid or even feeding, patients who had deep venous catheters, etc. Our incoming products are absolutely not uniform but are derived in a context of a severely diseased patient. So, because the starting material is not uniform, the preparation is also not uniform, and hence never a routine. The current definition of **hospital exemption** means preparation of ATMP *on a non-routine basis* according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made product for an

[111] Key centres in the HGG-IMMUNO-Group: Leuven (Belgium), Wuerzburg, Homburg and Erlangen (Germany), Sofie (Bulgaria), Stockholm (Sweden), Oslo (Norway), Milan (Italy), Geneva (Switserland), London (UK).

individual patient. In the context described, the "*non-routine basis*" is not clear: each production process with different incoming product situations make each product preparation unique, hence non-routine. Nevertheless the treatment as such should of course be aimed to be implemented ultimately as standard treatment.

But there is more. Cell products are produced and used in the hospital under the exclusive professional responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made product for an individual very ill patient. These patients, however, mostly need multiple treatment modalities of which the cell-based therapy is only one element. So the team of medical practitioners in the highly specialized medical centres should have a much broader knowledge of pathology and treatment including treatment interactions, than just the production and administration of cell products. Such complete and often multimodal treatment approach should be called **Advanced Therapy Treatment**.

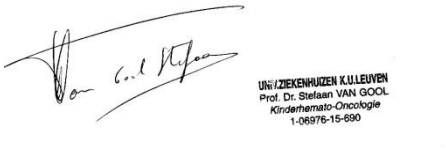
To allow and even facilitate life-saving **Advanced Therapy Treatment**, for which European highly specialized medical centres have now world-leading positions, one should define a niche for which specific regulations are needed. The niche should be defined as patients with low incidence clinical situation who need a multidisciplinary complex often multimodal treatment in a highly specialized medical centre and in whom full standardisation needs some flexibility. For this niche, one should develop and define the concept of **Advanced Therapy Treatment**. **Innovation in legislation** is needed for this: we need specific rules which are different to industry and pharmacy rules and which respond to the medical need that highly specialized medical centres nowadays can solve on a highly personalized per patient non-routine basis. We need a **license for advanced therapy treatment under the control of the Member State** rather than a **marketing authorization** for a cell product**.** The rules should be compatible with the clinical reality: the small number of patients, the personalization of the **Advanced Therapy Treatment**, the fact that the product is used within the hospital and does not come on the market.

Besides the *definition of the concept* of **Advanced Therapy Treatment**, which in no way is in concurrence with the development of ATMPs, but which gives answers to niche indications within highly specialized medical centres, one should consider the *costs* of the regulations. The personalized character of the **Advanced Therapy Treatment** inherently prohibit broad distribution in the community and hence risks to the community. Adapted rules which take into account the clinical reality should lower the cost. We should be aware that the legislator on the one hand increases rules and thereby costs; but there is no money available for research with such high costs, so the translational research decreases and the implementation of innovative treatment is blocked. Increasing rules and costs without having the money available for the patients means less accessibility and possibilities to reach innovative treatments. Hence increasing rules and costs results in less chances for cure for patients and less medical progression in Europe. The rules and the costs should be adapted to clinical reality and realistic needs. One should not forget, at least in our case, that patients surviving now for more than 10 years after relapsed grade IV malignant glioma, have been treated with cell products not produced under GMP and not under the current legislation. Unrealistic rules and costs cannot prohibit in future chances for cure for concrete patients. New legislation on **Advanced Therapy Treatment** should open possibilities for innovative and effective cell-based therapies for these niche indications with reality-adapted and appropriate rules on treatment and quality control and hence reality-adapted costs.

Patients and relatives nowadays are fully aware of the problems that we face.

In conclusion, we are entering a time which holds fantastic medical progression in Europe. In this medical progression, highly specialized medical centres have specific tasks in translational medicine and development but also conduction of innovative treatments. There is a niche for which only highly specialized medical centres can develop and conduct innovative **Advanced Therapy Treatments** without marketing. Adapted rules from innovative legislation are needed to regulate the **Advanced Therapy Treatments**. **Advanced Therapy Medicinal Products** and **Advanced Therapy Treatments** are in no way concurrent as both are aimed as innovative treatments for specific medical conditions. Europe should keep its current leading position for **Advanced Therapy Treatment**.

The ideas of this presentation, of which the slides are also included in the mailing, have been presented at the Workshop on Advanced Therapy Medicinal Products, Brussels, 20 February 2013 in the Directorate General for internal policies, policy department A: economic and scientific policy. The Workshop was chaired by co-chairs of the Health Working Group, Glenis Willmott and Alojz Peterle, MEPs. Part 1 of the Workshop was titled: **Advanced Therapy Treatment: The Future for Healthcare**. This title purely describes the need for innovative legislation to make this a reality, in favor of our patients suffering from diseases belonging to the niche clinical situation that is described.



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