Public consultation on the regulation on advanced therapy medicinal products – Contribution from Biofarmind (Netherlands association of Biotechnological, Pharmaceutical and Life Sciences Industry)

Biofarmind appreciates to contribute to the public consultation on the regulation on advanced therapy medicinal products. The comments of our association address the topics included in the public consultation paper. Biofarmind would appreciate to be informed on and contribute to further and future processes regarding evaluation of the ATMP regulation.

Marketing authorisation application requirements for advanced therapy medicinal products.

Marketing authorization of ATMPs should comply with requirements described in directive 2001/83/EC. This directive originally focused to regulate small organic molecules in general does not provide the regulatory framework needed for legislation of complex ATMPs. The requirements as described in the directive 2001/83/EC in general provide a disproportionate regulatory framework for ATMPs. This disproportionality hampers the development of ATMPs and strongly reduces scientific and medical progression which ultimately also affects marketing of these products. It should be noted that a frequently heard comment states that bone marrow transplantation could never have developed into a successful medical treatment if it would have been required to comply with a strict regulation similar to what currently applies to ATMPs. The validity of this comparison can be challenged and debated but the signal that goes with it should be taken into consideration. In fact many of the ATMPs are more closely related to medical treatment than they would relate to medicinal products as for example small organic molecules. The effect of the disproportionality can clearly be observed with a class of products that before the ATMP regulation were applied for medical treatments but nowadays are considered medicinal products that reside under the 2001/83/EC directive. Currently some of these products were unsuccessfully filed for a Marketing Authorization Application (MAA) which leads to disappearance of these treatments. Instead of ensuring a high level of public health, medical treatments that meet a medical need are disappearing or negatively impacted in their development.

Currently only a centralized procedure can be followed to gain marketing authorization. The assessment procedure of these MAAs was initially designed for small organic molecules. The current procedure is not proportionate. Firstly many ATMPs are developed for treatment of very small patient groups (orphans). Clinical trials are based on small patient populations that negatively impact the approval process. It should be considered to develop an alternative approval system for ATMPs as these products in many cases more resemble a medical treatment than they would fit into the definition of a medicinal product. Another difference with small organic molecules relates to the characteristics of the product itself. Small organic molecules but also many biologicals can be produced in large batches. This allows a stringent manufacture,

control and release. In contrast to this many ATMPs but in particular cell therapy products are produced for an individual patient based on autologous cells. This causes a high product variability that may be reflected in the clinical trial results as well. As in addition clinical trial evidence is in many cases built on studies including only a limited number of patients it is evident that this will impact on the benefit risk assessment when that is performed using current models that are based on experience gained with small organic compounds. Consequently a disproportionate evaluation is performed that in many cases would prevent market approval for ATMPs. The ATMP field but also its future patients would benefit from an approval system that takes into account the characteristics of the products, the small patient populations and the orphan status of the indications. The ATMP field requires a proportionate licensing system, which should facilitate development of safe and efficacious ATMPs allowing medical treatment progression. Currently ATMP development, marketing and treatment options are negatively influenced by applicable legislation. It is suggested to investigate and develop a proportionate adaptive licensing system that fits ATMP treatment in order to ensure a high level of public health.

The past MAA procedures illustrated a discrepancy between conclusions and opinions reached by the CAT versus CHMP. EMA has not succeeded to explain the different opinions and the underlying process. It is not understood that an opinion reached by the CAT which should be considered EMAs expert committee on ATMPs can be overruled by CHMP. It is suggested that the position of CAT versus CHMP is evaluated and re-organized. Ideally this should lead to an increased mandate for EMAs ATMP experts represented in the CAT

Requirements for combined advanced therapy medicinal products.

Currently experience with ATMPs is mainly focusing on gene and cell therapy. Also research and development pipelines seem to focus largely on products that would be classified as gene or cell therapy. Therefore it may be expected that future MAAs most likely will be dominated by gene and cell therapies. It is considered too early to evaluate the specific requirements for combined advanced therapy medicinal products. However it is anticipated that the suggested proportionate adaptive licensing process may also have a beneficial effect on development and licensing of combined ATMPs. It is suggested that combined ATMPs will be assessed on a case by case basis. As such it may be too early to develop specific guidelines for combined ATMPs as these most likely may hamper development options instead of providing the support that is currently needed.

Hospital exemption.

Hospital exemption procedures are delegated and performed by national authorities. This results in an unwanted un-harmonized implementation. In a number of countries, the eligibility criteria for hospital exemption are applied liberally, while the exempted products do not have to adhere to the same standards as centrally approved products. This undermines a central and harmonized assurance of quality, safety and efficacy of ATMPs. In addition some member states still fail to present a clear hospital exemption procedure. Assessment of hospital exemptions on the national level causes large differences among member states. Inconsistent implementation of the hospital exemption in the Member States and routine preparations of treatments under an exemption

impede the development of new safe and effective treatments. Harmonized and transparent European approach is crucial to bring more innovative, effective and safe therapies to all European patients. In case a product is exempted via the hospital exemption procedure it can be used only in a single member state which prevents availability of therapies for the European community at large. It should be questioned whether health benefits may be restricted to national markets. It is believed that the hospital exemption limits development of products to a level that these can be filed for MAA. As such the hospital exemption may have a counterproductive effect on development of products preventing or at least limiting marketing of products at central level which is the only route to assure availability of therapies to the European community at large. Consequently market sizes will be too small to return on investment which negatively affects development of innovative products. Furthermore it is anticipated that parallel circuits of nationally exempted products with in many cases lower standards presents a barrier for the development of non-exempted products by causing unfair competition.
Hospital exemption as described in the ATMP regulation requires an individual medical prescription for a custom made product for an individual patient. Knowing the nature of the ATMP product groups including the indications and the way these are manufactured the hospital exemption may not be used for gene therapy products as these mostly will be manufactured batch wise meaning that the patient based criterion cannot be met. Consequently hospital exemption does not equally facilitate all ATMP product categories.

It is concluded that the hospital exemption should be re-considered. Both authorized and exempted ATMPs should provide similar health benefits for the patients which are undermined by the current hospital exemption procedure. The hospital exemption procedure should guarantee a benefit to all eligible patients in Europe. It is considered crucial that the European Regulation is implemented in a harmonized way in all of the Member States. Only a full harmonization of hospital exemption procedures would provide a transparent and harmonized use without unwanted and unfair competition. Furthermore, hospital exemptions should no longer be allowed when a fully validated, centrally approved ATMP is available.

Incentives for the development of advanced therapy medicinal products.

Scientific advice is an important incentive that is available to companies involved in developing ATMPs. The benefit of scientific advice guiding development of an ATMP product is acknowledged especially since many of the small companies are not always familiar with regulatory requirements. It is observed that companies in many cases also liaise with national authorities for advice procedures. It is observed that national authorities not always include MAA requirements when providing their advice. Consequently the advice of some national authorities has been incomplete, insufficient and sometimes inappropriate with a view of aligning early development and early clinical trials to requirements that should be met at the MAA phase. As such national authorities that are not particularly involved in the MAA process should be made aware of MAA requirements which they should translate into the national advices.

Classification of ATMPs is supporting companies to determine which regulatory requirements should be met when development of their product continues. Although the classification has not

in all cases been logical in general it is believed that this incentive is providing the support that currently is sought by the field. However, the current ATMP product groups may need reconsideration. The relevance of gene and somatic cell therapy products as different ATMP classes is appreciated. But it can be debated whether the class of tissue engineered products should be maintained. It is suggested to evaluate the possibility to combine the tissue engineered products with somatic cell therapy products into one ATMP class.

According to CAT reports only two certification requests have been received and evaluated by CAT. Currently the certification process is not presenting any benefit. Nevertheless it is believed that certification may play a role in an adaptive licensing procedure which could benefit companies as well. However, this process would need EMAs assessment and opinion on Module 3 and Module 4 filings in advance of complete MAA submission. It could be worthwhile investigating whether this would benefit development of ATMPs and facilitate companies in the MAA process. It is believed that the certification process when changed and implemented in the adaptive licensing process may become more relevant and even stimulating to the development process of ATMPs.

Scope and adaptation to technical progress.

The scope of the regulation is to regulate ATMPs intended to be placed on the market. As described the regulatory framework is adopted from the regulatory framework that is designed to regulate medicinal products derived from small organic molecules. Considering the large differences between these product classes the adopted regulatory framework is currently limiting development of ATMPs. It is observed that the ATMP regulation abandons products used for medical treatment simply because the initial treatments are no longer allowed as due to the ATMP regulation these treatments became medicinal products residing under the medicinal product regulation 2001/83/EC. As such it can be questioned whether the ATMP regulation is over-regulating an earlier existing medical practice. Authorities are requested to investigate into a different approval system for ATMPs that would fit the specificities of ATMPs and the indications they are aiming to treat. An alternative adaptive licensing system should be developed in order to guarantee a proportionate approval process taking the nature of ATMPs and their use into sufficient consideration.