Public consultation on the regulation on advanced therapy medicinal products - Comments from the national expert group on ATMPs, the Netherlands

Introduction

In the expert group governmental organisations (Ministry of Health, Health Care Inspectorate, Medicines Evaluation Board, and Central Committee on Research involving Human Subjects), academic researchers and delegates from the innovative industry as well as patient organisations are represented. At a national level the main stakeholders are represented by this expert group.
The Netherlands welcomes the evaluation of the regulation on ATMPs and a future Commission report on the application of the Advanced Therapy Regulation.

This commentary does not necessarily reflect the views of the individual organisations.

2.1 Marketing authorisation application requirements for ATMPs

The ATMP regulation was issued with the aim to facilitate the development and licensing of advanced therapies within the European Union. Whereas the legal structure in the pharmaceutical legislation is well suited for the development and registration of small organic molecules, it is less suited for Advanced Therapy Medicinal Products. After all, ATMPs often resemble medical practice being performed in a hospital, which are not comparable with pharmaceutical (chemical) products being produced, tested, released and distributed to pharmacies or drugstores.

To solve the issues, guidelines have been developed to support the applicants in submitting their marketing-authorisation applications for human medicines. However, the culmination of legislation and guidelines has become an overdecorated Christmas tree.

Moreover, at this moment the expert group signals that the CAT as expert committee advising the CHMP for the specific scientific areas relevant to advanced therapies is not utilized to the full extent, leading the CHMP unintentionally to repeat the CAT's efforts. EMA's initiative to improve alignment and synergy between CAT and CHMP is acknowledged and welcomed. However, it is regarded a due task of the Commission to evaluate the intention and outcome as laid down in the Regulation.

Based on the requirements of the current Regulation, a Marketing Authorisation can only be obtained via the Centralised Procedure and is aiming at SMEs. However, not only the amount of data that must be generated for a small group of patients (note that many ATMPs are orphan drugs) is problematic. It is acknowledged that CHMP has high standards when it comes to required data to justify a positive benefit-risk of licensed products, including ATMPs. Many ATMPs are currently being developed within the setting of 1 academic hospital linked to 1 product facility. Treatment of patients with these new ATMPs is hospital-based with a less international character than the traditional pharmaceutical products that can be distributed throughout the EU. In the clinical trial setting, in which one small hospital based production facility, cultures cells for use in the same hospital, treatments could be successful in the future. However, successful expansion to the European scale is rarely seen. And the development of second/third generation ATMPs is essential for innovative therapy.

A phased Marketing Authorisation whereby a procedure used in one hospital, obtains a European approval, would be helpful. After approval a Marketing Authorisation Holder could always decide to up scale production and distribution; meanwhile patients can be treated in the “authorised” hospital (as is often done in orphan diseases anyway, or when treatments are provided by a centre of excellence). In addition, the reimbursement agencies-health care insurances will be able to recognise that the treatment has been a positively evaluated on benefit risk assessment by the CAT/CHMP. Such a stepwise approach with a European benefit risk assessment facilitates further development over time. This would provide an intermediate step between the ‘local’ hospital exemption and a fullscale centralised registration.

The Netherlands would be in favour of one Common Technical Document or its electronic version eCTD to facilitate submission for Marketing Authorisation Holders and provide them with one fixed format. If direct links could be made between the contents (sections) of the CTD and the long list of requirements a more transparent structure could be provided, i.e. in the form of an annotated CTD.

2.2 Requirements for combined ATMPs

As yet, very little experience has been gained with combined ATMPs. It is recommended to postpone setting requirements to a time when it is better known which products are going to be developed.

2.3 Hospital Exemption

Fact is that the number of ATMPs, whether submitted, registered, applied under Hospital Exemption or in clinical trial conditions has not met its expectation. The number of registered or submitted Marketing Authorisations is rather small and similarly is on a national basis for the hospital exemption. However, a moderate number of clinical trials with ATMPs is on-going within the Netherlands. Apparently these products are not moved forward to the market (i.e. Hospital Exemption or CP) following the clinical trial phase. Whereas centralised licensing might be a big hurdle for SMEs or academic institutions, Hospital Exemption is not always feasible following clinical developments. In the Netherlands a Hospital Exemption license is limited to a maximum of 10 patients.

In addition, the lack of a formalised Benefit/Risk assessment in the Hospital Exemption precludes reimbursement by Health Care Insurers in the Netherlands. It is conceivable that a small scale treatment setting – as envisaged in the Hospital Exemption – but linked to a formal benefit risk assessment by the CAT/CHMP, would be helpful for the definition of reimbursement schemes for those treatments.

Many academic researchers perform trials as proof of principle in a long process of advancing medicine, and not with the aim to develop and license a product. Therefore smallscale use for treatment needs to be further facilitated. This issue needs to be addressed in the future revision of the Regulation by introducing a kind of proportionality principle.

There are large discrepancies between the EU Member States in regulating early access of patients to ATMPs in the clinical context: therapeutic experiment and experimental therapy. The Netherlands would be in favour of a more harmonised interpretation of the Hospital Exemption. An option for harmonisation would be more adaptive or stepwise evaluation of

the benefit-risk of ATMPs with iterative phases of gathering clinical evidence followed by regulatory evaluation and would support the inclusion of upscaling into the paradigm for Adaptive Licensing.

2.4 Incentives for the development of ATMPs

The vast majority of companies developing ATMPs are SMEs or spin-offs of universities, with little or no knowledge on the regulatory requirements.

A derogation for SMEs as an incentive in their kick-off towards a registration is supported by the Netherlands, however, if the registration is finalised, the Marketing Authorisation Holder has to fulfil all legal requirements. Postapproval, an SME should fulfil the same legal requirements as every MAH. The expert group underscores that in practice it is still a big challenge, albeit all the support from EMA and NCAs for an SME to submit via the Centralised Procedure and fulfil the legal European requirements. A reduced fee for a SME will not be the solution nor will it be an incentive for innovative ATMPs.

Several incentives exist for the development of ATMPs.

- Scientific advice
- Scientific recommendation on advanced therapy classification
- Certification of quality and non-clinical data

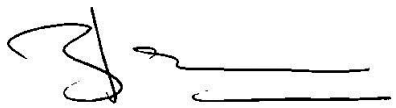
The first two incentives definitely benefit SME's. In addition scientific advice should be focussed on the regulatory aspects of effective submission by a MAH. However, certification has proven to have little or no benefit in the support of future Marketing Authorisation if an SME has an opportunity to out-licence or sell its product under development to another company there is no incentive to certify the data.

The company buying the product will necessary repeat all or at least the critical experiments in its own certified laboratories to verify the data and bring it in line with its own R&D standards and requirements.

2.5 Scope and adaption to technical progress

The definitions of somatic cell therapy and tissue engineered products should be merged as in single category to avoid endless discussion on classification. Defining the difference is extremely difficult and time consuming and has to be conducted on a case by case basis.

On behalf of the national expertgroup on ATMPs in the Netherlands,



Prof. Dr. H.G.M. Leufkens