Responses to the public consultation on the regulation on Advanced Therapy Medicinal Products (ATMP)

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On behalf of the academic and hospital teams contributing to the translational research and development of cell-based and gene transfer medicinal products.

2.1. Marketing authorisation application requirements for advanced therapy medicinal products.
Please provide your comments on the requirements for marketing authorisation applications set out in the Regulation.

The three criteria of Quality, Safety and Efficacy, for the assessment of ATMPs, prior to grant a marketing authorisation, are well acknowledged and accepted, as ATMPs have bee qualified as medicinal products. As any other medicinal products, it is well appreciated that ATMPs should be proposed to the patients only when they have been proven to be safe and efficacious, with an appropriate production system yielding a consistent product of satisfactory quality.
However it is at the level of requirements and "amount of data" that the regulation could be considered today as not enough adapted to ATMPs and not taking into account some necessary adaptation.
Some modulation should be considered in the application of these Q, S and E criteria. There are many situations where adaptation could be introduced and it would be too long to discuss all of them. However, particularly for the non clinical aspects, there as still too many uncertainties on what is expected by regulators and what will be objected at the time of MAA. The same holds true for Efficacy criteria where new methodologies could be further developed and encouraged for establishing evidence of efficacy in the context of small population, rare disease, autologous situation, lack of validated surrogate markers for chronic diseases for which only very long term follow-up could provide the clinical evidence. Currently it is not sure that those who take the risk of developing such complex ATMPs, and particularly academics and other non profit institution, have enough regulatory visibility.
The notion of "risk-based approach", which is supposed to help determining the amount of data to be provided in the respective part of the application dossier, has only been recently introduced (very recent development of the guideline). This approach could be seen as an improvement and encouragement for those who are investing a lot of resources, although for most of them the resources are very limited despite very good expertise. However, there is not yet sufficient experience to know how this "risk based approach" will be implemented by the regulators who have the last word at the time of the marketing authorisation.
At the time of marketing authorisation, a more "adaptive" approach, taking into account the disease, the target population, the type of product, etc. could be a way to modulate the amount of data to be generated to cover the requirements laid down in the Regulation.
A more progressive stepwise approach could be envisaged, particularly for ATMPs which are developed for rare disease or unmet medical needs, and some waivers or orthogonal methodologies could be envisaged with no prejudice for the safety of the recipients, which is the ultimate goal of both developers and regulators.
The question of "amount of data" has not only to be considered at the time of MAA but also all along the development cycle of the product and particularly for clinical trials at critical steps of the clinical development (first administration, pivotal trials) where, depending on the developer (academics in most cases for early phase) and depending on the type of product (autologous vs allogeneic, frozen product vs product for immediate use) it may be sometime necessary to take into account specific situations not envisaged in the current regulation.

It is well acknowledged that currently the clinical trial authorisation (CTA) is in the remit of the MS. It could however be of interest to consider some harmonisation and optimisation on the amount of data needed, at the time of CTA, so that at the time of MAA there is no gap or no divergent approach for the three Q, S and E criteria.
Finally, there is one specific point, in the quality area, for genetically modified cells or tissues dealing with the difficulties to draw the line between what is the "medicinal product" (covered by the MA requirements and responsibilities of the qualified person) and the "end product" to be administered to the patient, after extemporaneous ex vivo manipulations. According to part IV of annex I (as amended by Dir. 2009/120) at paragraph 3.2.1.2 " The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use.". However, there are some practical incompatibilities with this definition of active substance and final product, in the case of autologous cells or tissues which have to be genetically modified ex vivo with a vector (plasmid, non viral, viral) and immediately re-administered to the patients. Clearly the last step cannot take place at the "manufacturing site" declared in the MA dossier and the "release" of the end-product (i.e. the cell-based product to be administered to the patient) cannot be put under the responsibility of the qualified person, unless imposing that the QP is almost at the bedside to release extemporaneously….
Other examples, in the domain of cell-based or tissue-engineered products could also be considered, where there is a need for a "last step" of preparation of the end-product to be carried out (buffer exchange, thawing and re-suspension, etc…) prior to administration.
This difficulty in terms of "distinction" between drug substance, drug product, vector, in vivo or ex vivo use could be a huge obstacle for some products to reach the centrally authorised status of ATMP and will confine them into "local" regulations (and disharmony) and this is not the hospital exemption (discussed further) that will help resolving this difficulty.

2.2. Requirements for combined advanced therapy medicinal products.
Please provide your views on the authorisation procedure foreseen in the Advanced Therapy Regulation for combined advanced therapy medicinal products.

AP-HP has no experience so far with the development of "combined ATMP" and, as such, has no immediate and specific comment on this aspect.
However, considering the current legislation and according to the question "… the applicant must demonstrate that the essential requirements of the specific legislation on medical devices have been complied with ….", one could argue that it is not by "piling up" two regulations that the evaluation of a combined product will be strengthened. Indeed, it is very likely that in most cases, the medical device incorporated in the ATMP will not have been developed (and CE marked) for the intended use in the combined ATMP. Very likely the developer will make use of such a CE marked medical device simply because it was already available on the market and will use it for another use different from the one officially declared in the CE mark… (recent examples of such situations could be taken from the list of classification opinion granted by CAT, as published on the EMA website).
One could thus question the relevance of the "essential requirements" in the assessment of the final combined ATMP, at the time of MAA where even more complex questions such as "compatibility, stability of the combined product, etc…" will have to be covered by the applicant of the combined ATMP.

2.3. Hospital exemption.
Please provide your views on the application of the hospital exemption.

From the AP-HP point of view and based on many exchanges with other academic teams, there seems to be some problems with implementation of hospital exemption (HEx) in the various member states (MS) with even sometime confusion with the stage of development.
The HEx should not be a refuge for some products for which the developer did not manage (for economical or any other reasons) to get the sufficient "amount of data" to file a satisfactory dossier for the centralised evaluation system, as imposed by the ATMP Regulation. Such products, authorised locally could become competitors for other ATMPs which have fulfilled the EU requirements and gone through the EU centralised authorisation process.

On the other hand HEx status could be seen as a "temporary" status to allow the first stages of development. This status could be very valuable for academical/hospital projects, which could be handled at national level and under the supervision of national control authorities (so as to meet the objective of the Regulation in terms of traceability and pharmacovigilance for the safety of the patients). For such "national development plans", and particularly at the level of CTA, such products could be exempted of meeting some of the legal requirements, e.g. to be GMP certified investigational medicinal products, but produced by establishments authorised by the national control authorities.
HEx could thus be used as a regulatory process by academics and other non profit institutions, to progress in their translational research prior to any further development steps, most often in partnership with private pharma-compagnies, so as to end-up with a dossier fulfilling the complete set of requirements needed for a centrally authorised ATMP.
If this was not the intention of this HEx, then this should be clarified and other regulatory options should be open to allow academics to contribute at the very early stage of development of some "ATMP candidates" which are of no interest for private companies, be they SMEs or larger companies….
For instance, in France it is well acknowledged that many early phase clinical trials for those "ATMP candidates" are carried out by academic teams, using clinical materials produced in "hospital labs" which are not (and cannot be) qualified GMP insofar as in France only "pharmaceutical establishments" (as defined in the French regulation) are considered as "authorised establishment" and be granted the GMP certificate (provided that GMP inspection is satisfactory). This leads to the situation where most of the hospital teams which are producing their investigational ATMP candidate cannot fulfil the requirements laid down in the Clinical trial Directive…. and have to carry out their first stage clinical trials with clinical material, of quality but not qualified as GMP certified, with the risk of having their CT results not validated (for administrative reasons) in a future MAA dossier
Clearly a possible confusion in the intention of the HEx clause for the first stages of a clinical development for a product which is initially elaborated and developed by an academic team, and for which the level of GMP manufacture is not affordable…. To overcome this major difficulty (production of the clinical material for first stage clinical trials in GMP certified sites) there is a risk of transforming a coherent(and needed) clinical development under the "compassionate use" procedure using the so called "HEx materials"…
Clarification is needed on the exact intentions of the Hospital exemption, in relation with the intended framework of the ATMP regulation

2.4. Incentives for the development of advanced therapy medicinal products.
Please provide your views on the incentives provided for under the Advanced Therapy Regulation.

The incentives are not sufficiently adapted to the specific situation of hospital and other academic teams.
It is appreciated that most of the fees, due at the time of a scientific advice, or protocol assistance, or even MA submission, will be reduced for ATMPs. However, in terms of budget for the development of an ATMP, this is not only the fees for a given procedural step which have to be considered. As already explained in response 1, the very first limiting factor in the development of such complex products, for complex clinical situations, is the amount of data to be generated and summed up in a MAA dossier and the corresponding research budget. Clearly requirements for non-clinical and clinical development are getting more and more costly, not only because those studies have to be performed in accordance with GxPs (GLP and GCP namely) as well with materials GMP certified, which is also very costly, but because these studies are more and more complex to design, to validate and to be carried out in a timely fashion.
In addition some other incentives, and particularly "certification" have been laid down in the Regulation, only for SMEs, which is not a qualification accessible for hospitals.
This may lead to a possible unbalanced equity between products which are, at their early development stages, developed and produced by academics versus SMEs.
Clearly other types of incentives (not only fee reduction) should be envisaged, in a coordinated way with other European bodies (for example DG research) so as to coordinate efforts and sharing funds to allow appropriate European ATMP projects to be conceived and developed, up to the ultimate stage of being granted a marketing authorisation, for the greatest benefit of the EU patients.

2.5. Scope and adaptation to technical progress.
Please provide your views on the scope of the Regulation and in particular as to whether the scope should be modified to take account of technical progress.

The current definitions for cell therapy medicinal products and gene therapy medicinal products (two main classes of ATMPs) have already been modified since their first definition were laid down in 2003 (in amendment of Dir. 2001/83) and Tissue engineered products, as well as the notion of "combined ATMPs" (TEP) have been defined only in the 2007 ATMP Regulation.
This clearly shows that, due to scientific progress, other products (or derivatives from the initial three categories of ATMPs) could emerge and land in "borderline" or "grey zones", due to the complexity of the current definitions and difficulties to even "interpret" them.
As an example the cells which are derived from a completely closed preparation system and re-injected to the patient "within the same operating time" could escape from the ATMP regulation (because there is no "product" isolated nor formal production process in a dedicated facility), whereas the derived cells or products certainly pose the same type of questions, in terms of safety and efficacy.
Another example in the gene therapy field where the "genetic sequence", in the current definition, has to be "of biological origin" excluding any "synthetic sequence". There may be in the future some "gene therapy approaches" making use of synthetic genetic sequence, which will pose identical safety and efficacy questions (if even not the same uncertainties), but will be excluded from the ATMP definition and corresponding regulation/requirements.
There should be a system in place to allow rapid and relevant reconsideration/adaptation of the current definitions to take into account the scientific progress.
Regarding now the "requirements" laid down in the regulation, as already stated in response 1, it is clear that a more adapted and flexible approach should be envisaged so as to take into account the scientific progress and progressive better understanding of some technical issues, with the view to adapt the requirements at the various stages of developments and post-authorisation monitoring program.