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Union**

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Clinical Development of Gene Therapy Needs a Tailored Approach: A Regulatory Perspective from the European Union

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Abstract

Gene therapy is a rapidly evolving field that needs an integrated approach, as acknowledged in the concept article on the revision of the guideline on gene transfer medicinal products. The first gene therapy application for marketing authorization was approved in the International Conference on Harmonisation (ICH) region in 2012, the product being Alipogene tiparvovec. The regulatory process for this product has been commented on extensively, highlighting the challenges posed by such a novel technology. Here, as current or previous members of the Committee for Advanced Therapies, we share our perspectives and views on gene therapy as a treatment modality based on current common understanding and regulatory experience of gene therapy products in the European Union to date. It is our view that a tailored approach is needed for a given gene therapy product in order to achieve successful marketing authorization.

Introduction

FOR THE PROMISE AND POTENTIAL of a gene therapy medicinal product (GTMP) to be fully realized, it is important to understand and appreciate the relevant aspects of the science underpinning that product in order to apply these for the purposes of any regulatory scrutiny, such as for clinical trial or for marketing authorization.

The first gene therapy application for marketing authorization was approved in the International Conference on Harmonisation (ICH) region in 2012, the product being Alipogene tiparvovec (European Medicines Agency, 2012a). The regulatory process for this product has been commented on extensively, highlighting the challenges posed by such a novel technology (English, 2011; Flemming, 2012; Miller, 2012; Melchiorri et al., 2013).

Gene therapy, along with cell-based products, is regulated in the European Union (EU) as an advanced therapy medicinal product (ATMP) [as in Regulation (EC) No. 1394/2007]. The Committee for Advanced Therapies (CAT), which is the expert committee formed in 2009, to evaluate ATMP in the EU, has since dealt with several products at various stages of development, as part of European Medicines Agency (EMA) scientific advice or marketing authorization application (MAA). In addition, CAT members take part in informal meetings with ATMP developers, organized by the Innovation Task Force of EMA. The learning from regulatory procedures related to gene therapy products will be used to highlight the potential challenges that are applicable in general. Where possible, advice on how to negotiate some of the clinical challenges will be discussed. The purpose of this article is

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to highlight potential problems that developers should be aware of when intending to gain regulatory approval, that is, marketing authorization, and enable them to take appropriate steps to prevent or resolve these. The scientific principles, however, apply during the entire development cycle.

Concept for a Novel Gene Therapy and the Intended Effect

In general, gene therapies currently developed are intended either for correction of a genetic defect (monogenic diseases) or for other chronic conditions such as malignant tumors or chronic cardiac failure. The modes of action of such therapies mostly rely, for example, on production of therapeutic proteins by the transgene(s) or genetic modification of cells taking part in immune responses against cancer, as applicable. It is worth noting that vaccines against infectious diseases are excluded from the definition of gene therapy in the EU [as in Regulation (EC) No. 1394/2007 and Directive 2009/120/EC]. Compared with conventional medicines, which are often given on a repetitive basis, gene therapy is intended to be given fewer times, in some instances as a single administration, but their effect is intended to be long lasting, in principle even lifelong. There is thus usually little or no scope for correcting errors in dosing or administration. This introduces a significant challenge in determining the appropriate dose and posology to ensure that it will be safe and effective in the long-term.

Another problem that is common to biologics in general is the potential for immunogenicity, which in turn can affect subsequent administrations where there could be a need for repeated administration. This could influence not only the choice of the vector for gene delivery, but also the selection of the therapeutic protein to be expressed. In this respect, immunogenicity against the vector and immunogenicity against the expressed protein have to be distinguished. The former may be amenable to short courses of immunosuppression and/or appropriate choice of vector (e.g., one where there is negligible background immunity in the general population); the latter may be amenable by careful selection of patients, for example, for a genetic defect in those who express the protein but in a nonfunctional variant. Their immune system will not see the protein as “foreign” and likely be tolerant, thus decreasing the chances for an unwanted immune response. The final decision on both vector design and patient selection will be, in turn, based on the clinical indication and other available therapy options.

The route of administration needs to be carefully considered. Most conventional medicines are given systemically, either orally or through systemic injection/infusion. Gene therapy, on the other hand, is often considered for *in vivo* administration to the site of abnormality, for example, liver, muscles, and tumor sites, or *ex vivo* to the relevant tissue/cells. This introduces additional challenges in actual delivery. The feasibility of administration in clinical setting and the potential for sustained and clinically meaningful gene expression should drive the decision on the delivery route/method. This may, however, result in practical challenges, for example, the acceptability for the patient to receive multiple injections, finding an appropriate clinical trial design (mock injections and their ethical acceptability), or

how to measure local expression of the gene. The latter may in a locally administered gene therapy not always result in a (sufficiently) positive signal at the site of injection, for example, in cases where the biopsy is taken from an area at the edge of the radius of the previous injection.

If the gene therapy product is to be given concurrently with other medicinal products, the potential interaction between the treatments might affect the efficacy and safety of the medical therapy and should be considered in regard to the choice of other medicines and the timing of their administration.

Vector design

Depending on whether a temporary or persistent therapeutic effect is expected, different methods and vectors for gene delivery may be utilized. Plasmids and nonintegrating viral vectors are considered to be less risky than integrating lentiviruses and retroviruses that may be capable of causing insertional mutagenesis in the recipient cells. More recently, however, integrating vectors have been redesigned to make them safer. One potential drawback of nonintegrating vectors is the lack of long-term effect, necessary for treatment of monogenetic diseases; however, their effect in tissue with very slow turn over (e.g., skeletal muscle) may last for months and, in some cases, for years. From a regulatory perspective, claims for longer-term expression would have to be substantiated and clearly explained.

Changes to vector design may be introduced during development to maximize the efficacy/safety profile of a GTMP, following preliminary evidence of the relevance of the concept and/or strategy in nonclinical and/or clinical studies. Examples of such modifications include change of promoter or vector serotype, introduction of tissue-specific enhancers, or other genetic changes that will change the characteristics of the product. A timely evaluation of the impact that such changes might have on the safety and efficacy profile of the product is beneficial for the developers as it may reduce the number of bridging studies that might be requested when applying for a new clinical trial or marketing authorization. In addition to the expected comparability exercise on product quality, pertinent regulatory issues include the extent of additional nonclinical studies required in conjunction with the introduced change, the relevance of nonclinical models used, and the need for additional nonclinical data to support bridging of the new product for further clinical trials (reflection paper EMA/CAT/GTWP/44236/2009).

Manufacture and testing

Overall, the production of GTMPs shares many aspects of conventional biologicals (such as vaccines) or biotechnologically derived medicinal products. Special attention should be paid to the starting materials of a gene therapy product, for example, cell banks, viral seed stocks, helper viruses, and plasmid preparations. It should be kept in mind that such biological materials are able to carry microbiological contaminants, introduced at any upstream steps (particularly during the research stages where the potential of these materials has been identified), which may be very difficult to remove at later stages of production. The batch sizes are usually sufficiently large and the products can be

stored, for example, frozen, enabling proper in-process and release testing.

The main difficulties are encountered in establishing potency tests for gene therapy products, especially where complex modes of action for the product is expected (e.g., cancer immunotherapy products). The need for developing functional potency assays is dependent on the level of information gained with other methods, for example, transgene expression and expressed product activity, and how well consistency and comparability issues can be addressed with the other assays available. Vector infectivity assay might provide useful supporting information in addition, but is currently considered to be of limited value.

Manufacturing changes and their impact

It is not unusual for a complex biological product such as gene therapy to be produced at pilot scale initially with subsequent changes or adaptation for scale-up for commercial purpose. In some cases, it may also be necessary to improve the vector and/or production cell line before commercialization. What is often not appreciated is the impact that the change(s) can potentially have on the quality and, as a consequence, on the efficacy and safety of the product. Some changes may be considered minor as they will have no impact on the final product (e.g., changes in standard raw materials such as basic culture media), whereas other changes (e.g., change in vector design or the production cell line—see the section Vector design) could have a significant effect on the safety and/or efficacy profile that is difficult to predict without additional data. Therefore, a comparability exercise (according to principles of ICH Q5E and guidelines on comparability of biotechnology-derived medicinal products after a change in the manufacturing process—nonclinical and clinical issues EMEA/CHMP/BMWP/101695/2006) is needed to identify the potential differences in the quality, safety, or efficacy profile induced by the proposed change and to reassure that they will have no clinically meaningful impact. A clinical study to establish such comparability can be costly and time-consuming as the study will need to be sufficiently large and sensitive to exclude clinically relevant differences. Therefore, it is advisable that any change in the vector design or in the process that could have a major impact on the product profile should be made before pivotal trials, if possible. This is especially important if changes to the vector and/or the production cell line are foreseen, as they may lead to direct changes in safety and efficacy of the treatment through, for example, altered cell target and transduction, expression level of the therapeutic protein(s), and level of (and possibly new) impurities. Overall, changes in the starting materials and the resulting GT product are considered most critical and should be justified by additional data before further clinical trials and at the time of the MAA.

Where clear differences at quality level are detected after the change has been made, a risk-based approach (European Medicines Agency, 2011) should be taken to evaluate and address the possible effects on efficacy and safety. These identified risks should be built into the rest of the clinical program, including the risk management plan. It is advisable to carefully plan the design of the product early in the development as it is critical for later success.

Scope of nonclinical experiments

In general, the more complex and specific to humans a product is, the more challenging it is to define appropriate nonclinical studies, and in particular, to define relevant animal models. As GTMPs are complex products, feasibility of conventional nonclinical safety testing is often limited. Gene therapy nonclinical studies are to be preferably performed on suitable animal models, for example, natural mutation, knockout animals, if available. *In vitro* models such as diseased cells could be an alternative, if justified, or could be an additional element in the nonclinical development. Toxicity and biodistribution studies can be challenging, for example, because of different tissue tropism of the vector in animal and human tissues or because of the activity of the transgene product in these species. Thus, appropriate design of biodistribution studies has to be considered carefully in the development of a GTMP and the same holds for toxicity to predict clinical outcome as closely as possible. For example, using a vector with animal transgene might be more useful to study pharmacological toxicity instead of human transgene product or in addition to it. Further, since the product of the human transgene(s) may induce immunogenicity in animals, it may be appropriate and relevant to use viral vectors encoding an animal transgene in a homologous animal model.

To circumvent possible immunogenicity issues of the transgene product it might be helpful to use an immune-deficient animal model in biodistribution studies. In addition, it may be important and necessary to perform intravenous administration of the viral vector in biodistribution studies to model worst-case scenarios. The duration of biodistribution studies should last sufficiently long to cover the presence of and the expression from the vector, even accepting the limitations of achieving this comprehensively, in case of the clinical need for lifelong vector persistency of that product. Possible dissemination of a viral vector to nontarget tissues or organs should be addressed by analyzing the presence of viral vector genome in a wide range of tissues and body fluids, and this requires the use of highly sensitive and adequately validated detection assays. If research-grade materials are used, these should be as comparable as possible to the clinical-grade materials.

In principle, animal testing is generally considered necessary for GTMPs before human trials, as is usually the case for medicine's product development, after taking the above issues into account in planning the scope of the nonclinical experiments for a given gene therapy product. In some cases where hazards, specific risks, and risk factors have been identified based on known risks associated with the nature of the product, findings observed in proof-of-concept studies or *in vitro* testing, it could be justified that additional animal testing would not further substantiate the risk. In these cases a risk-based approach might be used as a rational tool for justification and the specific risk could be mitigated with appropriate clinical measures. For example, assessment of immunogenicity and its impact will need to be mainly studied in humans as there may be no suitable animal model. Moreover, alternative methods need to be developed such as meaningful *in vitro* assays for tumorigenicity testing to support nonclinical development and adequate evaluation of a GTMP. In this respect, induced pluripotent stem cell

technology may provide a unique opportunity to generate disease phenotypes in a Petri dish for use as *in vitro* model systems, as promising alternative to animal models, where applicable. Even if an *in vitro* system cannot adequately represent all aspects of a multifaceted disease, the ability to generate any human tissue or cells could provide a useful alternative to address specific aspects where the gene therapy is intended to be delivered to an organ for therapeutic purpose.

The sufficiency of nonclinical approach chosen, for example, whether primarily based on animal transgene or in combination with use of immune-deficient animals, will need to be justified and evaluated on a case-by-case basis, and it might be advisable to seek scientific advice. Recent analyses of EMA scientific advice procedures suggest that, in general, regulatory guidance is a good starting point, as they highlight the main concerns to be addressed during development, but a more tailored nonclinical approach to gene therapies may have to be employed (Vestergaard *et al.*, 2013).

Phases of clinical development

Traditional clinical development is based on specified phases, often described in terms of phases 1–4. These phases evolved based on experience gained primarily from development of small chemical molecules. Phase 1 would typically be to study pharmacokinetics (PK), pharmacodynamics (PD) tolerance, and preliminary safety. Phase 2 would cover proof of concept and dose finding. Phase 3 is usually pivotal and confirmatory, with phase 4 being post-approval. Not all of these phases and objectives might apply for a specified gene therapy product in exactly the same way as conventionally intended. For a gene therapy, the clinical development plan needs to be tailored in order to provide the best scientific evidence. In a rare disease, it is acknowledged that, to ensure resources are used diligently, it may not be possible to follow traditional clinical development phases. In such situations, it is advisable to discuss with regulators if it is acceptable to deviate from the standard phases and study multiple aspects of the treatment in fewer trials to generate adequate evidence for regulatory approval. Where appropriate, it might be necessary to build in long-term efficacy evaluation through ongoing studies as part of postapproval commitment as a pragmatic alternative to a very long preapproval trial, if it can be justified.

Whichever development plan is considered appropriate and chosen, it is important to ensure that as much evidence relating to efficacy and safety, both short-term and long-term, is gathered from all the patients exposed to the given gene therapy product—ideally as early as from phase 1 trials. This will ensure that maximum amount of evidence can be generated and all potentially valuable clinical data are collected. Further, this will also ensure that sponsors comply with the need for long-term data on efficacy and safety as required by ATMP regulations.

Role of concomitant interventional procedures

Where a gene therapy product needs to be administered to a specified anatomical site, this might be achievable only through an invasive procedure. The procedure itself might have an influence on the efficacy and, perhaps more importantly, on the safety of the product. It is important to be

able to delineate the effect of the procedure as distinct from the effect of the product itself. For example, if there is a complication such as inflammation, infection, or bleeding, it might not always be clear whether it is attributable to the product or the procedure. It is important to have a reasonable estimate of the complication rate attributable to the procedure itself. It would also be important to consider evaluating the ability of the procedure to deliver the product optimally in a preclinical setting where feasible, accepting its limitations that possible complications that occur in patients may not be apparent in preclinical animal models.

Feasibility of using a comparator

An ideal confirmatory trial would have a comparator with a randomized, double-blind design. In the case of a gene therapy using an invasive procedure for delivery, achieving such an ideal design might be impractical, and possibly unethical. However, an open-label trial with or without an active comparator has the potential to introduce bias, possibly invalidating the conclusions. It is important to ensure that sufficient safeguards are built into the analysis plan to minimize bias. For example, it might be necessary to use experts not involved in the trial to conduct a blinded review of findings.

Where a valid active comparator is not available, it is possible to have standard of care as comparator. However, if the standard of care is highly variable, it can make it difficult to interpret the clinical findings. Uncontrolled, single-arm trials are not encouraged for confirmatory trials as it can be extremely difficult to interpret the findings. If such a trial is at all planned as a pivotal confirmatory trial for licensing purpose, for example, in serious diseases with no other treatment available where ethical objections might make it difficult to have a comparator arm on no active therapy, regulatory advice should be sought before embarking on such a trial to ensure such a study can be considered valid. Proceeding with such a trial without regulatory input could also be considered as unethical.

One possible solution in such a situation is to collect a careful and sufficiently long record of the clinical history of the patients before treatment that includes repeated, periodic measurement of relevant surrogate markers of the disease, where available. This may help to evaluate if the effect of the treatment is likely to be real and that the findings are not merely because of random fluctuations that occur as part of the natural history of the disease or because of improvement attributable to closer medical monitoring for the enrolled patients.

How to choose the end point(s)

Proper end points is one of the most critical aspects in a clinical trial. The choice of the end points will depend on its purpose. In early stage trials, it may be acceptable to use end points that are not necessarily reflective of clinical benefit but are sensitive alternatives that could help with planning further development. These include surrogate end points, biomarkers, and pharmacodynamic end points. Even in these situations, validated end points would be preferable but not usually mandatory.

In order to demonstrate clinical benefit, appropriate, clinically relevant end points will need to be chosen. In many common diseases this can be straightforward as accepted end points exist, for example, overall survival or progression-free survival in cancers and American College

of Rheumatism (ACR) scores for rheumatoid arthritis. In other diseases such as diabetes or anemia (regardless of etiology), established surrogate markers are available. However, if no such established end point is available, as it can be the case with very rare diseases that may be good candidates for gene therapy, the most appropriate end point should be one that can be measured objectively and in a reproducible way. If such an end point is not available, a combination of more than one relevant end point may be a viable alternative. In addition, in the case of gene therapy, end points reflecting long-term persistence of clinical benefit should be part of end-point selection. This could include, in addition to clinical end points and where feasible (see below), evidence of persistence of gene like the expression of gene and levels of expressed protein(s). For example, such data together with data gathered from nonclinical and mechanistic studies on the relation of gene expression and the correction of a gene defect could be highly supportive for a more limited clinical dataset in case such clinical data are difficult to obtain. Again, such approaches would best be discussed with regulators in advance within a scientific advice procedure.

The need to develop and validate appropriate and relevant clinical/pharmacodynamic (bio) markers should be considered early in the life cycle to facilitate development. The clinical correlation of biomarkers should be considered carefully. For example, a drop in the serum level of creatine kinase may indicate that muscle deterioration has been reduced in muscular dystrophy by a given treatment, but may also indicate that the disease has progressed to such a point that there is little remaining muscle to be wasted.

In a complex multisystem disorder, which is a rare disease, an alternative approach that is different from a traditional approach based on a single or composite clinical end point(s) could be one based on the totality of evidence (see also Melchiorri *et al.*, 2013). This could include expression of the therapeutic gene (the transgene) and the levels of resulting protein, in addition to applicable traditional clinically relevant end points for the target indication. Such an approach could be preferable as it could provide important correlation between the various aspects of the outcome of the treatment with the product. However, for diseases of relatively inaccessible tissues such as heart or brain, this may be technically and ethically problematic. In other cases, such as skeletal muscle diseases, a biopsy may be feasible, but the potential risk of random sampling a tiny fraction of the tissue that may not reflect the general expression of the transgene in the whole tissue; that is, a negative result would not rule out gene expression.

Demonstration of long-term efficacy

Long-term efficacy is an important component of gene therapy. Further, as mentioned before, all patients who receive the product regardless of which phase of clinical development should be followed up postauthorization for long-term efficacy, in addition to safety, to fulfill the specific provisions laid down in the ATMP regulation. Patients who receive the product in a compassionate use or research program that is outside of commercial development should also be part of the total data set, where feasible, unless otherwise justified. Unlike traditional therapy for chronic diseases requiring multiple repeated administrations, gene therapy might be administered

only once. Although relevant short-term clinical outcomes might be sufficient at the time of filing for marketing authorization, demonstration of persistence of expression and therapeutic effect in the longer term would be expected. It may be possible to demonstrate long-term expression as part of postapproval commitment, if sufficient early evidence of positive clinical benefit is available to give an initial approval. The adequacy of the duration of expression, if not permanent, would be part of the overall clinical benefit–risk evaluation and is difficult to prescribe.

Immunogenicity

A common problem with biological medicines is the occurrence of immunogenicity leading to production of antibodies. With more complex biologicals such as gene therapy based on vectors, cell-mediated immunity can also develop. Such immunogenicity can compromise efficacy, as well as safety, by neutralizing the activity and/or possibly leading to immunologically mediated adverse events, though the latter are probably modest. Further, it can make repeated administration of the product not possible. Concomitant immunosuppression is a possible solution and is currently used routinely. Although immune suppressive treatments have been used safely over many years for organ transplantation, from a regulatory perspective it is important to ensure that its value with a given gene therapy product is established clearly during the development. For example, unless supported by data from nonclinical/clinical studies, routine use of immunotherapy for adeno-associated virus vector-based gene therapy may not be of value and is not encouraged (Bryant *et al.*, 2013). A risk-based approach (European Medicines Agency, 2011) is needed to evaluate the potential for the development of immunogenicity and the resultant effect before planning the appropriate solution. In addition, the actual clinical consequence of such immunogenicity, whether antibody or cell-mediated, will need to be carefully assessed. The mere presence of antibodies, for example, may not negate the value of the product if continued clinical benefit is present. In such a situation, the relevance of the antibodies will need to be carefully evaluated as part of the overall benefit versus risk. In some diseases, for example, monogenic diseases, the risk of developing immunogenicity could be reduced by ensuring that a detectable level of the expressed endogenous protein is present before therapy. For the first gene therapy authorized in the EU, the indication was indeed restricted to patients with detectable levels of the protein to be replaced by the gene therapy (as in European Medicines Agency, 2012b).

Repeat administration

The need for lifelong expression in case of treating inborn errors caused by defective genes puts additional expectation on such a treatment. If the effect were to wane after a variable period of time, the necessity of re-administration might arise. This is only possible if there is no/low immunogenicity after the initial administration, or where strategies that can circumvent such immune responses are available. Further, complex administration procedures might render repeat treatment clinically impractical. For example, repeated administration into an organ such as liver introduces increased risk of serious adverse events, which could have a negative impact on the benefit–risk assessment.

Safety

For a given gene therapy product, safety evaluation should be based on an individualized approach. A standard set of experiments that might be appropriate for the development of a small molecule could be inappropriate. As mentioned before, nonclinical experiments may have limitations in their applicability. In addition to general safety, specific aspects attributable to gene therapy need to be taken into account, such as oncogenicity and germ-line transmission. Risk of viral vector integration is discussed in detail in the CAT reflection article (Aiuti *et al.*, 2013). Germ line transmission remains a remote but possible event. The risks of viral insertion in germ cells are largely unexplored; thus, this possibility should be avoided.

Long-term safety follow-up should be an integral part of the entire clinical development, including postauthorization follow-up. The risk management plan, which is a legal requirement in the EU at the time of marketing authorization, should contain details of the plans for collection of long-term safety for the entire population exposed, both within and outside the EU. This could include the use of patient registry. Safety assessment from a regulatory perspective is a life-cycle issue and continues postapproval. It is also well-known that comprehensive data on safety of a medicine are rarely achievable preapproval from clinical trials alone and need real-life usage and increased exposure before they can properly be assessed. What is important is that all patients who received therapy, even in early stages, will need to be followed-up for this purpose. The longer the follow-up needs to be, the more systematically it needs to be planned and organized.

Conclusions

In general, development of a given medicinal product would follow tried-and-tested path, which can ensure a degree of consistency with other products. However, the unique biological properties of gene therapy dictate careful consideration of the many different aspects so as to tailor the development that is fit for purpose (European Medicines Agency, 2009). The regulatory expectation is that such development is based on sound science rather than merely following a set tradition. The concept of risk-based approach (European Medicines Agency, 2011) has been developed for this reason. If in doubt, early consultation with regulatory authorities is recommended. In the authors' opinion, it is never too early to seek advice from regulators.

Disclaimer

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

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