Considerations on paediatric investigation plans for advanced therapy medicinal products

Authors
David Uguen, Voisin Consulting Life Sciences, France, and Cécile De Coster, Voisin Consulting Life Sciences, US.

Keywords
Advanced therapy medicinal product (ATMP); Gene therapy medicinal product (GTMP); Cell therapy medicinal product (CTMP); Tissue engineered product (TEP); Regulation (EC) 1901/2006; Paediatric investigation plan (PIP); Marketing authorisation application (MAA).

Abstract
In Europe, advanced therapy medicinal products (ATMPs) are subject to the requirements laid down in the Paediatric Regulation. A company developing an ATMP must therefore obtain agreement from the EMA on a paediatric investigation plan (PIP) or waiver prior to submitting its marketing authorisation application (MAA). Because ATMPs are different from ‘conventional’ medicinal products, defining the appropriate paediatric development plan for an ATMP necessitates fully taking into account the particular nature of the product, its innovative mechanism of action and potential risks relating to its use.

It requires the involvement and close collaboration of experts covering the regulatory, quality/CMC, nonclinical and clinical fields.

Introduction
In the last decade, advances in cellular and molecular biotechnology have led to the development of gene- and cell-based medicinal products, offering new opportunities to treat severe diseases and cover therapeutic needs. In the EU, these innovative products were initially regulated on a national basis. Because of their complexity and technical specificity, the EU member states agreed that specially tailored and harmonised rules were needed to ensure the free movement of these products within the Community. This is the reason why a new Regulation was developed for ATMPs (Regulation (EC) 1394/2007). This was implemented on 30 December 2008, and amends Directive 2001/83/EC and Regulation (EC) 726/2004. Among other elements, this Regulation confirms that ATMPs are medicinal products – this implies that they are subject to the requirements laid down in the Paediatric Regulation (Regulation (EC) 1901/2006).

More precisely, the ATMP Regulation defines three separate categories of advanced therapies: gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (CTMPs) and tissue engineered products (TEPs). The Regulation expects these products to be evaluated by the European Medicines Agency (EMA) and receive a Community marketing authorisation, except in cases where they are prepared as custom-made products, to comply with an individual medical prescription for an individual patient. When such products are manufactured and used within the same member state, and administered in a hospital under the exclusive professional responsibility of a medical practitioner (a ‘hospital exemption’), a national registration scheme applies.

Despite the fact that only one ATMP is registered at the Community level to date, a number of nationally registered ATMPs are currently on the European market and a multitude of new ATMPs are being developed. For those products already marketed legally in the EU, the ATMP Regulation contains transitional rules; these products must comply with EU rules no later than 30 December 2011, with the exception of TEPs, for which compliance will be required no later than 30 December 2012.

The Paediatric Regulation requires that any MAA for a new medicinal product includes the results of studies performed in compliance with an agreed PIP and/or a waiver or deferral, which cumulatively cover all subsets of the paediatric population. The same requirement applies to applications related to authorised medicinal products – if these are protected by a supplementary protection certificate (SPC) or by a patent which qualifies for the granting of the SPC – when authorisation for a new indication, new pharmaceutical form or a new route of administration is sought.

Contrary to other types of medicinal products (generics, hybrids, biosimilars, products of well-established use, homeopathic and traditional herbal medicinal products), ATMPs are not exempt by Directive 2001/83/EC from the obligation to submit a PIP (or waiver) application. Any company developing or marketing an ATMP in the EU must therefore have some knowledge of the Paediatric Regulation and the PIP requirements.

Regulatory considerations
For ATMPs which, on 30 December 2008, were legally on the Community market (in accordance with national or Community legislation), the ATMP Regulation requires that an MAA be submitted to EMA by 30 December 2011 for GTMPs and somatic CTMPs and by 30 December 2012 for TEPs. At the time of the MAA submission, compliance with an approved PIP is required for already marketed ATMPs that were granted a marketing authorisation in accordance with the Community pharmaceutical legislation after 26 July 2008. The same applies to ATMPs already marketed on 30 December 2008 which have not been granted a marketing authorisation in accordance with the Community pharmaceutical legislation (ie, were registered on the basis of national legislation). Considering that the mean time for obtaining a PIP approval is approximately ten months, one would assume that companies which have to comply with the above MAA submission deadlines have already obtained agreement on their PIP (or waiver) application. It seems, however, that no PIPs relating to already marketed ATMPs have yet been approved by EMA (see below).

For new ATMPs – ie, products which are in development, the situation is clearer: if they are not custom-made products (as described earlier), they must obtain a marketing authorisation in compliance with the Community Code. For this, an MAA has to be submitted to the EMA for assessment by the Committee for Advanced Therapies (CAT), a multidisciplinary group of European experts who are specialists in the
assumption of quality, safety and efficacy of ATMPs, and the Committee for Medicinal Products for Human Use (CHMP). Prior to submitting this MAA, it is mandatory to:

- Submit an application for a PIP and/or a request for a deferral or waiver
- Obtain agreement from the EMA
- Conduct the studies which have been agreed to in the approved PIP (if relevant).

To date, only a handful of PIPs relating to new ATMPs have been agreed by the EMA.

Approved PIPs for ATMPs

As of June 2011, the EMA has issued positive PIP decisions for a total of four ATMPs. In addition, the agency has refused a PIP application and granted a product-specific waiver on its own motion for an additional ATMP. The main characteristics of these PIPs/waiver decisions are summarised in Table 1.

Drawing conclusions – even preliminary ones – on the basis of only five EMA decisions would be premature. However, it can be noted that, so far, two positive PIP decisions relate to TEPs, one PIP concerns a somatic CTMP and one PIP concerns a GTMP. All approved PIPs include specific paediatric clinical studies, two out of the four approved PIPs include specific nonclinical studies and none of the approved PIPs include specific quality studies. All EMA decisions allow one or more studies contained in these PIPs to be deferred. Overall, it has taken between three and 12 months from the date of submission of the PIP application to the EMA decision date.

PIP strategy for an ATMP

We have explained in a previous article that defining the right PIP strategy (ie, defining how, cumulatively, the PIP +/- waiver +/- deferral combination will cover, for each targeted indication, all subsets of the paediatric population in a way that is both acceptable from a regulatory standpoint and in line with the applicant’s registration plans and expectations) can be a complex exercise for which a structured, stepwise approach can be useful. This approach can be applied successfully to the design of PIP strategies for ATMPs.

A company developing a new ATMP, as for any other medicinal product, must first check whether the Paediatric Regulation applies. As already discussed above, this will be the case for the great majority of ATMPs, except those prepared for an individual patient on a non-routine basis and for which a national registration scheme will apply.

Second, the company will need to determine whether a waiver or a PIP (or a combination of both) applies to its ATMP. To answer this question, it is important to check whether the condition that is targeted by the ATMP is included in the EMA list of class waivers. For example, for the EU registration of sipuleucel-T (Provenge, an autologous immunotherapeutic CTMP approved by the FDA on 29 April 2010 as the first autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer), the applicant will not need to submit a PIP considering that this ATMP is intended for the treatment of prostate cancer, a condition which is listed as a class waiver. While no PIP is required, a confirmation of applicability of a class waiver should be obtained from the EMA Paediatric Committee (PDCO) before submitting an MAA in the EU. Outside of this list of class waivers, an ATMP may be granted a product-specific waiver in cases where at least one of the grounds defined in Article 11 of the Paediatric Regulation applies: if the ATMP is developed for the treatment of a condition which does not occur in paediatrics, or if it can be expected that, in the paediatric population, the ATMP (1) will not show efficacy, (2) will not be safe, or (3) will not bring significant therapeutic benefit compared with existing treatments. The EMA decided for example that this latter ground applied to the ATMP containing allogenic ex vivo expanded umbilical cord blood cells and developed for the treatment of different haematological cancers (see Table 1). (Note: for children under 12 years of age, graft of cord blood stem cells has proven to be effective). It is important to note that these grounds can apply only to a subset of the paediatric population (eg, from birth to less than two years) – in these cases a partial waiver is requested, and a PIP must be defined to cover the rest of the paediatric age range (ie, from two years to less than 18 years).

In the case where a PIP must be defined, the applicant must choose between two main approaches: either to conduct the paediatric studies before submitting the MAA or to defer the start and/or completion of these studies until after application for marketing authorisation (a combination of both approaches being possible).

There are cases where requesting a deferral for paediatric studies will not make sense in the frame of a PIP for an ATMP. This is typically the case for ATMPs targeting paediatric genetic diseases which develop at (and often before) birth. An example would be ATMPs developed for the treatment of severe combined immunodeficiency (SCID). This group of inherited disorders is characterised by little or no immune defence response due to the total or partial lack of lymphocytes. This deficiency usually results in the onset of one or more serious infections within the first few months of life. Due to these recurrent infections, children with SCID fail to grow and to gain weight as expected – this is therefore a chronically debilitating and life-threatening disease. Several ATMPs are currently being developed against SCID. One of them is a GTMP which consists of CD34+ cells transfected with a vector containing the adenosine deaminase (ADA) gene. It will be used for the treatment of SCID due to ADA deficiency. For this type of ATMP, the development is ‘paediatric’ by nature: the drug is conceived from the beginning to treat solely children. Therefore the content of the PIP shall describe the entire content of the future MAA, covering the CMC, nonclinical and clinical aspects in a comprehensive manner.

There are other cases where the ATMP is developed to treat both adult and paediatric patients. An example of this would be a somatic CTMP made of tumour cells (presented in the form of lysates and living cells) and aimed at treating glioblastoma. Glioblastoma is the most common primary malignant brain tumour; however, glioblastoma in children is less common than in adults, and little is known about its clinical outcome in young patients. In such a case, the content of the PIP would be different; it is reasonable to think that the PDCO would accept, or even recommend, that such a medicinal product is tested in adults first and that all paediatric studies be deferred until a positive benefit-risk ratio is demonstrated for the product in adults. Also, in this instance, it could be appropriate to recommend a step-wise deferral approach, in which, once shown to be useful in adults, the product would need to demonstrate positive results in the older paediatric subset (eg, 15 to <18 years), before being tested in younger patients (ie, <15 years).

The Paediatric Regulation foresees that a deferral may be granted in two specific cases: (1) when it is appropriate to conduct studies in adults – and so increase the knowledge of the product – prior to
<table>
<thead>
<tr>
<th>Active Substance (type of ATMP: cells/gene/ tissue)</th>
<th>Condition(s)</th>
<th>PIP decision date (time from PIP submission to decision)</th>
<th>Waiver (grounds for)</th>
<th>Approved PIP studies</th>
<th>Deferral as part of PIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus-mediated Herpes Simplex Virus –thymidine kinase gene (GTMP)</td>
<td>High grade glioma</td>
<td>23 May 2008 (~3 months)</td>
<td>Birth - &lt;1 month (absence of significant therapeutic benefit as clinical studies not feasible)</td>
<td>One clinical open-label uncontrolled safety study in patients (1 month - &lt;18 years) with high grade glioma</td>
<td>Yes</td>
</tr>
<tr>
<td>Allogenic ex vivo expanded umbilical cord blood cells (TEP)</td>
<td>i) Acute lymphoblastic leukaemia ii) Acute myeloid leukaemia iii) Chronic myeloid leukaemia iv) Myelodysplastic syndrome v) Hodgkin’s disease vi) Non-Hodgkin’s lymphoma</td>
<td>22 Dec 2009 (~6 months)</td>
<td>Mandatory waiver for all conditions: Birth - &lt;12 years (absence of significant therapeutic benefit) 12 - &lt;18 years (absence of significant therapeutic benefit as clinical studies not feasible)</td>
<td>Not applicable (PIP was refused)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Expanded human autologous mesenchymal adult stem cells extracted from adipose tissue (somatic CTMP)</td>
<td>i) Anal fistula of cryptoglandular aetiology ii) Anal fistula of Crohn’s disease associated aetiology iii) Non-inflammatory anal fistula</td>
<td>19 Feb 2010 (~8 months)</td>
<td>For conditions i) &amp; ii): Birth - &lt;4 years (absence of significant therapeutic benefit as clinical studies not feasible) For condition iii): Birth - &lt;18 years (medicinal product likely to be ineffective)</td>
<td>One nonclinical biodistribution study in rats One clinical open-label, long-term trial to assess the activity and safety</td>
<td>Yes</td>
</tr>
<tr>
<td>Autologous cartilage derived cultured chondrocytes (TEP)</td>
<td>Cartilage disorders</td>
<td>6 May 2011 (~12 months)</td>
<td>Birth – (age of) closure of the femoral epiphyseal growth plate (absence of significant therapeutic benefit)</td>
<td>One clinical study covering the retrospective investigation of safety and prospective investigation of safety and efficacy in paediatric patients treated for cartilage defects with ATMP</td>
<td>Yes</td>
</tr>
<tr>
<td>Autologous oral mucosal epithelial cells (TEP).</td>
<td>Limbal stem cell deficiency (LSCD).</td>
<td>23 May 2011 (~ 11 months)</td>
<td>Birth - &lt;2 years (Absence of significant therapeutic benefit or fulfilment of therapeutic need)</td>
<td>One nonclinical single-dose toxicity study in rabbits One open-label clinical study to assess safety, tolerability and activity of ATMP in LSCD patients (2 - &lt;18 years).</td>
<td>Yes</td>
</tr>
</tbody>
</table>
initiating studies in the paediatric population and (2) when studies in paediatric patients will take longer to conduct than studies in adults. As shown in Table 1, all positive PIP decisions approved to date relate to conditions affecting both adults and children, and all of them include deferred studies. Considering the innovative and complex nature of ATMPs, it makes sense indeed to test them first in adults and to defer paediatric studies where possible. It should be noted that, however, that when agreement for a deferral is sought, at least a synopsis of the study to be deferred is required as part of a PIP application to PDCO. Any information not provided at the time of the initial PIP application must be strongly justified.

Guidance for paediatric development
To help in the preparation of a PIP or waiver application, the EMA offers guidance and advice to applicants via two regulatory procedures:

- Scientific advice in relation to the paediatric development of the product can be sought from the EMA. This is an opportunity to obtain feedback from the agency on the design and conduct of studies necessary to demonstrate the quality, safety and efficacy of the medicinal product in this specific patient population. Gaining such advice prior to a PIP application can be very valuable to check that the studies to be proposed in the PIP are adequate, in particular at an early stage of the medicinal product development. In contrast to the PIP procedure, seeking advice from the agency is not mandatory; also, the measures defined in a PIP are binding on the MAA applicant, whereas the advice received is not binding. Of note, scientific advice on paediatric questions is provided free of charge. For ATMPs, requesting scientific advice on paediatric issues prior to submitting a PIP application can be particularly relevant, for example when products are developed to treat paediatric genetic diseases. In these instances, CAT members are involved in the scientific advice procedure (several members of the CAT are also part of PDCO).

- Requesting a pre-submission meeting with EMA prior to submitting a PIP application can also be very useful. This is an opportunity to discuss issues related to the definition of the paediatric condition, the completeness of the draft PIP dossier, the appropriateness of the submission timing or to obtain preliminary feedback on the acceptability of the proposed paediatric strategy. In the case of ATMPs, pre-submission meetings allow presentation of the specificities of the product and its innovative mechanism of action to the EMA paediatric team, and to familiarise the agency with the intended development plan. These meetings usually help with the validation of the subsequent application.

Timing for PIP submission for an ATMP
The preparation of the PIP needs to be planned into the development of a new medicinal product from a very early stage. The Paediatric Regulation specifically mentions that a PIP (or a waiver) application shall be submitted “not later than upon completion of the human pharmacokinetic (PK) studies in adults”. In the case of conventional medicinal products, this often means the PIP must be submitted to PDCO when the Phase I studies have been completed. In contrast, with ATMPs, and with TEPs in particular, generation of PK data is rarely straightforward, and sometimes not feasible. A relevant example would be an ATMP developed to treat diabetic foot ulcers and consisting of fibroblast grafts seeded onto a biodegradable matrix. Such a product is designed to adjust to the wound environment and to provide growth factors and other substances that may be lacking in chronic wounds. Grafted cells are not expected to be distributed within the human body, therefore conventional PK studies cannot be conducted (a biodistribution study in animals is usually required). In such a case, more advanced clinical studies might be necessary to provide interpretable and informative data that will help for future paediatric development. The optimum time point for submitting PIPs for ATMPs should therefore always be determined on a case-by-case basis.

Scientific aspects and other considerations
Designing a successful paediatric development programme requires the involvement and close collaboration of several experts covering the regulatory, quality/CMC, nonclinical and clinical fields. In the case of an ATMP, specific scientific expertise on the product is necessary. Understanding the mechanism of action of the product, its biological properties, and how it will interact with the patient’s body is key, especially in paediatric patients in whom the biological functions are sometimes different from those in adults (and even different from one paediatric subset to another).

The risks associated with these types of products are also of particular importance to build an adequate approach for their development in the paediatric population. For ATMPs, the concept of risk-based approach, as defined in Annex I, part IV of Directive 2001/83/EC should be applied, including in the paediatric development. This approach is based on the identification of risks inherent to the nature of the ATMP and associated with its quality, safety and efficacy. Risk factors are usually related to the nature, the biological activity and the method of administration of the ATMP. They are also linked to the patients to be treated (this is particularly relevant in the case of paediatric patients) and to the environment (which can influence the phenotype, migration pattern and other characteristics of the cells). Adequately identifying all of the product attributes, including the potential reactivity to the environment, and integrating these into the risk profile of the ATMP is key to justify its development.

Specific clinical aspects
To be of benefit to paediatric patients participating in the clinical research – and beyond this to the rest of the paediatric population – clinical studies must be properly designed to ensure the quality and interpretability of the data obtained. Considering the peculiarities of the paediatric population and, at the same time, the innovative nature of ATMPs, it can be very complicated to design appropriate trials which can generate informative and interpretable results. The following elements should be considered:

- The paediatric population cannot be considered as a single and homogeneous population; as a result, the definition of the appropriate population for a first-in-human trial is sometimes difficult.

- Because of the peculiar nature of ATMPs, and their specific mode of administration, conducting a clinical study in healthy subjects is generally not feasible, nor is it ethically conceivable.

- Several ATMPs are developed for rare diseases, for which no treatments may be available, therefore eliminating the possibility to conduct comparative trials.

- In most instances, the use of placebo as comparator is not appropriate (this would be the case, for example, of a TEP intended to be grafted onto the patient’s eye). When a comparator can be identified, a double-blind design is rarely possible.
Some ATMPs, especially those which are expected to achieve robust functional and structural integration into the patient’s body, require (very) long-term safety and efficacy assessment
with adults or older paediatric patients to the youngest patients relies on the biological and tissular similarities between the different population subsets. Although the age at which the child’s eye becomes comparable to that of an adult is not precisely established, the cornea is known to continue developing during the first years of life and the ocular tissue is estimated to start behaving like that of an adult around the age of ten years. For such products, it is thus not possible to extrapolate adults’ data, and a specific paediatric clinical development plan must be designed.

**Nonclinical considerations**

Elaboration of the paediatric development of ATMPs is complicated by the fact that the nonclinical package can never be as reliable and comprehensive as it would be for a conventional medicinal product. This is due to the fact that defining an adequate nonclinical package to support a first-in-human clinical study for an ATMP is particularly challenging. A major issue relates to the choice of the relevant animal models. For example, the use of stem cells is currently being investigated to treat juvenile macular degeneration. However, because of anatomical differences, no adequate animal models can be identified to prove the therapeutic concept or to assess potential safety issues. Indeed, the commonly used rodent models in research do not possess a macula. Another major concern is that most animal models do not allow envisaging all aspects of the multiple mechanisms of action of ATMPs. For instance, one of the investigational strategies to treat diabetic retinopathy relies on the administration of stem cell via intra-ocular injection. In animal models, while pro-oedema can occur, proliferation of cells is not observed.

When moving to paediatric development, this can become even more challenging. Standard nonclinical studies using adult animals, or safety information from adult humans, cannot always adequately predict the safety profiles for all paediatric age groups, especially reactions on immature systems such as the developing brain, the kidneys, or the pulmonary, reproductive or immune systems. The need for juvenile animal studies should thus be taken into consideration. When feasible, such studies can be used to investigate findings that cannot be adequately, ethically, and safely assessed in paediatric clinical trials. However, for products such as ATMPs, the feasibility of juvenile studies is questionable. For example, for ATMPs developed for the treatment of ocular diseases (which will typically be injected into the eye), the small size of the eyes of animals usually considered as representative paediatric models, render the conduct of these studies unfeasible. The use of large animals could potentially be considered, but would require testing the product on significant number of them to validate the model.

In summary, when designing the nonclinical section of the PIP for an ATMP, the difficulties associated with the limitations of the animal models – when they exist – and the risks resulting from the lack of information should be thoroughly discussed.

**CMC considerations**

When treating paediatric patients, access to an age-appropriate formulation is required to ensure safe and accurate dose administration, to maximise compliance and to reduce the risk of medical errors. As for any other medicinal products, the development of an age-appropriate formulation, covering a large range of patients, must be considered for ATMPs whenever possible. Liquid formulations, easily adjustable to all patients, usually represent the best option. Most ATMPs are formulated as a cellular suspension for infusion, and this formulation is expected to be adequate for this patient population. For other products, such as TEPs intended to be grafted, the development of an age-appropriate formulation is usually not feasible. When developing the paediatric formulation, one should also consider the use of appropriate excipients known to be safe and effective for the age of the paediatric patient. Similarly to adult patients treated with ATMPs, a strict control of the culture medium and additives is essential to ensure the safety of the final formulation.

**Conclusion**

Some ATMPs currently in development appear to be potentially promising treatments for serious and sometimes rare diseases affecting the paediatric population. With the entry into force of the ATMP Regulation, it has become mandatory for companies developing ATMPs to consider the need to prepare and submit a PIP. Although a very limited number of PIPs have been approved for ATMPs to date, one can be confident that this number will grow significantly in the coming years.

Designing an adequate PIP is a complex exercise during which all specifics of the product and the condition to be treated must be taken into account and considered in the context of the peculiarities of each paediatric subset. This can translate into a very challenging task for which expert advice is required and dialogue with regulatory agencies is recommended.

To the best of the authors’ knowledge, so far the EMA has not released any guidelines or recommendations to assist with the paediatric development of ATMPs. In the near future, it could be useful to organise a workshop during which regulators and ATMP developers could share their views on the specific issues associated with the paediatric development of ATMPs and possible ways to address them.

**References**

5. Assessment report for ChondroCelect, Common name: characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins; Procedure No EMEA/H/C/000878 (EMEA/724428/2009).
8. Communication from the Commission: Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2008/C 243/01).