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The risk-based approach to ATMP development – Generally accepted by regulators but infrequently used by companies

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ABSTRACT

Advanced therapy medicinal products (ATMPs) are the cutting edge of drug innovation. ATMPs have different challenges than other drug classes. To accommodate these challenges and facilitate science-driven development, flexibility in the requirements to demonstrate the safety and efficacy of this rapidly evolving drug class is necessary. To create flexibility, the European Union introduced the risk-based approach. This approach provides the possibility of omitting guideline-based studies based on risk analyses. To gain insight into the effect of the risk-based approach on the non-clinical development of ATMPs, two questions are addressed in this paper. Firstly, "Do companies use a risk-based approach for the non-clinical development of ATMPs?" and, secondly, "Does the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) accept non-clinical development programs based on the risk-based approach?" Scientific advice letters formulated by the CHMP were analyzed. The risk-based approach was used to justify deviations from the guidelines in the majority (75%) of the cases. The CHMP accepted 40% of the proposals to omit studies and stated that additional data was necessary to make an informed decision for 35% of the proposals. This indicates that the risk-based approach facilitates the science-driven development of ATMPs.

1. Introduction

Advanced therapy medicinal products (ATMPs), the cutting edge of drug innovation, hold promise to offer a cure for a variety of diseases for which there are no satisfactory therapies, such as cancer, inherited monogenic diseases, cardiovascular disease, Parkinson's disease, diabetes and arthritis (Jekerle et al., 2010; Jilma, 2010; Klug et al., 2012; Maciulaitis et al., 2012; Schneider et al., 2010; Vamvakas et al., 2011). ATMPs are diverse in nature, comprising gene therapy medicinal products (GTMPs)[1] and cell-based medicinal products (CBMPs) (including cell therapy[2] and tissue engineering)[3]. These products have different characteristics than small molecule and biotechnology-derived drugs. These differences entail that ATMPs also have a different risk profile and other challenges for safety evaluations, such as the effects of ineffective integration into to the patient's body systems, cells and genes and immune responses. Moreover, some ATMPs can stimulate tumor growth (Mavilio, 2012; Schneider et al., 2010).

To accommodate the development of this new class of pharmaceuticals, the European Union created regulation EC 1394/2007 on ATMPs and revised Directive 2001/83 on the community code relating to medicinal products for human use (Klug et al., 2012). As a general principle, ATMPs have to fulfill the same scientific and regulatory standards as other medicinal products (European Union, 2001, 2007; Jekerle et al., 2010; Klug et al., 2012; Mavilio, 2012). Nevertheless, regulation EC 1394/2007 together with the technical requirements contained in revised Annex I of Directive 2001/83/EC introduce specific requirements for ATMPs (European Union, 2001; Klug et al., 2012). These specific requirements are high level requirements because the type and amount of data necessary to demonstrate the quality, safety and efficacy of diverse of

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[1] **Definition of GTMPs:** *"Gene therapy products consist of recombinant nucleic acids administered to humans with a view to regulating, repairing, replacing, adding or deleting a genetic sequence, and whereby its effect relates directly to the recombinant sequence or the product of genetic expression of this sequence. Novel recombinant or vector-based vaccines against infectious diseases are also specifically excluded from the definition of gene therapy products"* (Jekerle et al., 2010, p. 6).

[2] **Definition of cell therapy:** *"Cell therapy medicinal products contain or consist of substantially manipulated cells and have properties for treating, preventing, or diagnosing a disease through the pharmacological, immunological and metabolic action of the cells or tissues"* (Jekerle et al., 2010, p. 6).

[3] **Definition of tissue engineering products:** *"It should be noted that it is the intended action (i.e., treating, preventing or diagnosis a disease for cell therapy medicinal products vs. regenerating, repairing, replacing a human tissue for tissue engineered products) that will differentiate a cell therapy medicinal product from a tissue engineered product"* (Jekerle et al., 2010, p. 6).

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ATMPs is highly specific (Jekerle et al., 2010). Sufficient flexibility in the development of ATMPs is important to anticipate the rapid evolution of science and technology in the field of ATMPs (Jekerle et al., 2010; Schneider et al., 2010). The technical requirements are therefore further explored in several class-specific guidelines of the EMA (Jekerle et al., 2010; Schneider et al., 2010).

To create more flexibility, the legislation and guidelines concerning ATMPs recommend companies to use a risk-based approach during development (European Medicines Agency, 2013; Klug et al., 2012; Jekerle et al., 2010; Cohen-Haguenauer, 2013). The EMA defined the risk-based approach as *"a strategy aiming to determine the extent of quality, non-clinical and clinical data to be included in the Marketing Authorisation Application (MAA), in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products and to justify any deviation from technical requirement as defined in Annex I, part IV of Directive 2001/83/EC"* (European Medicines Agency, 2013, p. 4). The purpose of the risk-based approach is to obtain a profile of the risks associated with the use of a specific ATMP by identifying the various risks[4] associated with the clinical use and the risk factors[5] inherent to the ATMP with respect to quality, safety and efficacy.

The risk-based approach is an ongoing process whereby the manufacturer conducts risk analyses at the beginning and during product development (European Medicines Agency, 2013; Jekerle et al., 2010). The amount of data required for MAA depends on the level of risk, state of knowledge about the product under development and experience of the manufacturer with other ATMPs (Cohen-Haguenauer, 2013). The final risk profile will take shape as a result of the consolidation of the identified risk factors (Cohen-Haguenauer, 2013).

The purpose of the risk-based approach in the development of ATMPs is to create a framework wherein it is encouraged to take into account continuously evolving science and technology in order to design a tailor-made ATMP development program. The approach aims to provide the possibility of moving away from guideline-based ATMP development and to facilitate science-driven development strategies of ATMPs. The risk profile of an ATMP can point out that some, requirements prescribed in the EMA guidelines or in the Directive 2001/83/EC are redundant and that other strategies are more relevant to establish the quality, safety and efficacy of the product under study (European Medicines Agency, 2013).

The aim of this paper was to study whether the risk-based approach facilitates science-driven non-clinical drug development. To gain insight into the effect of the risk-based approach at the level of non-clinical development of ATMPs, two questions are addressed in this paper. Firstly, *"Do companies use a risk-based approach for the non-clinical development of ATMPs?"* and, secondly, *"Does the Committee for Medicinal Products for Human Use (CHMP) of the EMA accept non-clinical development programs based on the risk-based approach?"*

Only three ATMPs have received market approval in the EU. This sample is too limited for an analysis of the drug registration dossiers of those ATMPs. We therefore analyzed the scientific advice letters formulated by the CHMP in order to gain insight into the use and acceptance of the risk-based approach for the non-clinical development of currently developed ATMPs. Companies can apply for scientific advice of the CHMP at every stage of product development. In their scientific advice request, companies can pose questions related to quality, non-clinical and clinical development. The Scientific Advice Working Party of the(SAWP) answers the questions in close consultation with relevant working parties such as the Committee for Advanced Therapies (CAT), the Biologics Working Party (BWP) and the Safety Working Party (SWP) and prepares a scientific advice letter including the background on the disease and the product provided by the company, the questions posed by the company and the answers formulated by the SAWP and adopted by the CHMP. The questions posed by the manufactures indicate if and how often manufacturers use a risk-based approach. The answer provides insight into if and how often the CHMP accepts non-clinical development programs using the risk-based approach.

2. Methodology

The scientific advice letters of the CHMP concerning ATMPs between 2009 and 2012 were accessed at the Dutch Medicines Evaluation Board. The letters wherein the applicant sought advice about non-clinical development were selected for this analysis. The questions in the section *"Questions on Toxico-Pharmacological Development"* were used to evaluate whether companies proposed non-clinical development programs using a risk-based approach. The answers to these questions were used to assess to what extent the CHMP accepts innovative risk-based non-clinical programs for ATMP.

The aim of the risk-based approach is to determine the extent of data necessary for a marketing application and to justify any deviation from the requirements. Questions that could be related to deviating from the standard requirements were included and attributed to the following categories: (1) questions that proposed to do no animal studies; (2) questions that proposed to do one or two animal studies; (3) questions that proposed to not do repeat-dose toxicity studies in animals (4) questions that proposed to not do carcinogenicity studies in animals and (5) questions that proposed to not do reproduction toxicity studies in animals. These categories were selected because using a risk-based approach to justify the omission of chronic animal studies is most interesting since these studies are the most time-consuming and expensive of the regulatory required studies. Questions which could not be related to these categories were excluded. To determine whether companies used the risk-based approach to justify omitting a study, the line of argumentation used by the manufacturer was analyzed. The line of argumentation to not conduct animal studies was classified as (1) based on a risk analysis when companies argued that based on current knowledge and/or available data, the study would be redundant, (2) not based on a risk analysis when companies used no argument or other arguments, for example that the study was not feasible.

To evaluate whether the CHMP endorses risk-based non-clinical programs for ATMP, the answers of the CHMP to the questions classified as risk-based were analyzed and referred to the following categories: (1) proposal not accepted, (2) more information is necessary to confirm the provided line of argumentation, (3) proposal accepted and (4) no answer. The ATMPs and manufacturers were anonymized.

3. Results

Between 2009 and 2012, pharmaceutical companies requested scientific advice 80 times for 66 different ATMPs of the CHMP. The scientific advice letters concerned 48 CBMP and 18 GTMP. Fifty letters (for 48 different products) included questions related to

[4] The EMA defines risks as *"potential unfavourable effect that can be attributed to the clinical use of ATMP and is of concern to the patient and/or to other populations (e.g. caregivers and offspring)"* (European Medicines Agency, 2013, p. 4). Examples of risks are: unwanted immunogenicity, disease transmission, tumor formation and treatment failure.

[5] The EMA defines risk factors as *"qualitative or quantitative characteristic that contributes to a specific risk following the handling and/or administration of an ATMP"* (European Medicines Agency, 2013, p. 4). Risk factors are associated with the nature of the product, biodistribution and manufacturing issues.