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Development of non-substantially manipulated cell-based ATMPs[1]: flexibility introduced via the application of the risk-based approach

1. SCOPE

This document aims to illustrate some of the possibilities and limitations of the risk-based approach using the example of an ATMP based on cells that have not been subjected to substantial manipulation and that are not intended for the same essential function: a de-novo development of autologous bone marrow or peripheral blood CD34+ cells for treatment of acute myocardial infarction. In the example, the cells are harvested from bone marrow or mobilized using cytokines followed by collection of the peripheral blood mononuclear cells by apheresis. The harvested cells are transported to a GMP facility and CD34+ cells are immunoselected. The cell preparation is administered to the patient by intracoronary injection without any freezing or storage step.

2. Introduction

2.1. What is aim of the application of risk-based approach for ATMPs and how does it impact on the dossier requirements?

Due to the specific nature of advanced therapy medicinal products (ATMPs), a risk-based approach (RBA) may be applied to determine the extent of the data that should be submitted in support of a marketing authorisation application (MAA).

Specifically, the risk-based approach permits marketing authorisation holders to adjust the content of the MAA having regard to the characteristics of the product, including the possibility of waiving some of the data/requirements that are typically expected when applying for a marketing authorisation. It is stressed, however, that the deviation from the standard requirements as laid down in Part IV of the Annex to Directive 2001/83[2]/EC and the relevant scientific guidelines needs to be duly justified.

While the RBA brings flexibility, it also implies that the marketing authorisation applicant is responsible to ensure that the content of the MAA is sufficient to demonstrate a positive benefit-risk balance. The

[1] For more information on what constitute non-substantially manipulated ATMPs, please consult the CAT Reflection paper on classification of ATMPs (EMA/CAT/600280/2010 rev.1).
Abbreviations: RBA: risk-based approach; ATMP: Advanced Therapy Medicinal Product; MAA: Marketing Authorisation Application; Ph. Eur.: European Pharmacopoeia; GMP: Good Manufacturing Practice; PoC: proof of concept studies

[2] Directive 2001/83/EC on the Community code relating to medicinal products for human use, (OJ L311, 28.11.2001, p.67).

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marketing authorisation applicant should consider all the potential risks related to the product on the basis of all information available, including an assessment of the potential implications for the quality, safety and efficacy profile of the product. The level of effort and documentation should be commensurate with the level of risk of the specific product.

The RBA may be applied to the full content of the marketing authorisation application / development or to specific parts thereof.

It is important to note that the RBA will have to be tailored to the specificities of the ATMP on a case-by-case basis (see 'Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products' (EMA/CAT/CPWP/686637/2011))

2.2. How can the RBA methodology be applied to the example product?

The matrix tables on the next pages are an illustration of the application of the risk-based approach for the example product using the methodology as described in the Guideline on the risk-based approach (EMA/CAT/CPWP/686637/2011)

The Questions and Answers in sections 3 to 5 of this document are based on the outcome of the RBA assessment.

It is important to note that these answers should not be construed as setting the dossier requirement for all ATMPs based on cells that have not be subject to substantial manipulation as the application of the risk-based approach requires a case-by-case analysis. Also, additional flexibilities might be justified based e.g. on prior experience with similar products, experience with the administration device(s) and/or published information. Lastly, this document is not intended to provide guidance on how to apply GMP requirements for this product or for non-substantially manipulated ATMPs in general.

RBA Matrix table for: Autologous bone marrow or peripheral blood CD34+ cells for the treatment of acute myocardial infarction.

Risk Risk factor / Quality	Tumour formation	Unwanted tissue formation	Unwanted immunogenicity	Disease transmission[3]	Treatment failure Lack of efficacy	Toxicity Safety issues
Cell starting material	Autologous cells, not substantially manipulated, are expected to represent no risk for tumourigenicity		Autologous cells are not expected to trigger immune reactions	For autologous product disease transmission to the recipient is not an issue	Quality and consistency of cells has to be ensured; harmonized procedures for procurement, handling, transport. Acceptance criteria for volume and cell numbers	In principle autologous cells are not expected to be associated with toxicity, but altered environment for cells has to be considered
Aspects of the manufacturing process and level of cell manipulation	Autologous cells, not substantially manipulated, are expected to represent no risk for tumourigenicity				The process should not introduce additional variability; the consistency needs to be ensured. Conditions for manipulation/handling before final product administration (including transport) need to be defined.	Safety of the product could be affected by the potential process-related impurities and microbiological contamination
Cell population, heterogeneity & differentiation potential	Autologous cells, not substantially manipulated, are expected to represent no risk for tumourigenicity		Autologous cells are not expected to trigger immune reactions	For autologous product disease transmission to the recipient is not an issue;	Quality and consistency of cells/mixture has to be ensured and monitored; Though the manufacturing is very limited, the cell selection process has to be validated	In principle autologous cells are not expected to be associated with toxicity, but altered environment for cells has to be considered

[3] The risk of microbiological contamination of the starting material during procurement and of the cells during manufacture should be minimized via appropriate procurement / manufacturing conditions.

Risk Risk factor / Quality	Tumour formation	Unwanted tissue formation	Unwanted immunogenicity	Disease transmission[3]	Treatment failure Lack of efficacy	Toxicity Safety issues
Genetic stability	Due to the non-substantial manipulation of cells, genetic stability is expected					
Structural / functional integrity					Potency assay needs to be established; functional & viability markers	
Ancilliary substances, devices & formulation	Impact on cells needs to be considered	Impact on cells needs to be considered	Possible immunogenicity of reagents and residuals has to be considered	Microbial purity has to be ensured	Impact on functionality of cells needs to be considered	Has to be addressed; should be in line with Ph. Eur. requirements

Risk Risk factor / Non-clinical	Tumour formation	Unwanted tissue formation	Unwanted immunogenicity	Disease transmission	Treatment failure Lack of efficacy	Toxicity Safety issues
Relevance of the animal model					Relevant animal models are available and (literature) data should be presented demonstrating PoC to support clinical efficacy data.	Consider potential safety issues related to altered cell environment, locally increased cell numbers and application/delivery system. Focus on large animal model and/or relevant literature data to address procedure-related safety issues; waiving of stand-alone toxicity studies justified. Address toxicity of reagents/residuals
Biodistribution	Cells not manipulated, short persistency justifies waiving of formal stand-alone tumorigenicity studies	Short persistency justifies waiving of formal stand-alone biodistribution studies			Consider to generate biodistribution data in PoC studies to support the proposed mode of action in the target population.	

Risk Risk factor / Clinical	Tumour formation	Unwanted tissue formation	Unwanted immunogenicity	Disease transmission	Treatment failure Lack of efficacy	Toxicity Safety issues
Patient-related			Unwanted immunogenicity of residuals to be considered in inclusion - exclusion criteria		Risk of treatment failure due to variable patient factors: age, reduced regenerative capacity, concomitant disease/morbidity resulting in impaired cell functionality,	Safety issues linked to patient age, morbidity, vessel/tissue fragility
Disease-related					Risk of treatment failure to be considered in relation to a) Biological activity, if not linked to pathophysiology of disease b) timing of administration post myocardial infarction c) suboptimal dose d) size of myocardial infarction	Cell-based product itself is not expected to cause toxicity. Consider safety issues related to altered environment and Cell dose.

Risk Risk factor / Clinical	Tumour formation	Unwanted tissue formation	Unwanted immunogenicity	Disease transmission	Treatment failure Lack of efficacy	Toxicity Safety issues
Medical procedure-related						Risk of procedure-related toxicity: Rupture of coronary artery, myocardial bleeding dependent on administration procedure. Device and procedure assessed in large animal studies or supported by scientific literature (see above)

3. Quality and manufacturing

3.1. What information about the quality and consistency of starting and raw materials should be provided, including donor testing?

In the example, the manufacturing process is relatively simple as there is no substantial manipulation of the CD34+ cells. Consequently, the quality of the final medicinal product is highly dependent on the starting material and raw materials[4] used during its manufacture. Therefore, the control of quality and consistency of the starting and raw materials is extremely important.

Commission Directive 2006/17/EC implementing Directive 2004/23/EC regarding technical requirements for donation, procurement and testing of human tissues and cells has to be complied with. It is expected that information on the apheresis procedure is available to the ATMP manufacturer for inclusion in the MAA. The maximum effort should be made to harmonise the procurement procedure at different clinical sites.

In the MAA the applicant should define the conditions of handling and transport of the starting material, which should be adequate to preserve the quality thereof.

Acceptance criteria for the donated materials are expected such as volume and cell numbers. Individual cell populations in the apheresis material, their viability and amount of desired CD34+ cells should be also monitored. As this is an autologous product, the specifications set in terms of the cell composition should take into consideration the intrinsic biological variability that may be expected in the treated patients.

As far as possible, raw materials should be in line with pharmacopoeial requirements, if relevant. (See also the general chapter of the Ph. Eur. on Raw materials for the production of cell-based and gene therapy products (5.2.12).) When non-compendial or research grade materials are used, the suitability thereof should be ensured.

Starting and raw materials should be free of microbial contamination. Additionally, a system ensuring traceability of starting and raw materials must be in place.

3.2. What information on the manufacturing process and its validation are required?

The manufacturing process, i.e. all steps after the bone marrow harvest or the apheresis, should be performed under GMP and described in detail.

In the MAA dossier, the applicant should provide evidence that the process is consistent and that differences in the final product characteristics are caused only by its origin (interindividual variability between patients).

For the example product, the manufacturing process is continuous, i.e. without holding steps at the level of intermediates or the drug substance. It will therefore not be possible to apply extensive in-process control testing during the manufacture

Additionally, there is very short time for release testing. Thus the release testing of the drug product may need to be adapted due to the nature of product (short shelf life and limited product availability).

[4] The definition of starting material and raw material is provided for in Part IV of the Annex to Directive 2001/83/EC.

Due to the above described limitations, process validation is key in order to build the assurance of quality (e.g. potency testing or proliferation assays may be performed after batch release as supporting data for process validation).

Information demonstrating that sufficiently low amount of process-related impurities (e.g. materials used during the separation process) are reached should be discussed, if they are not monitored within in-process or release testing.

For validation purposes, the starting material from healthy donors may be used, if sufficiently justified. For the process validation, steps before and after the manufacturing (e.g. transportation) should be taken into account.

If multiple manufacturing sites are identified in the MAA for the preparation of this product, identical equipment, manufacturing conditions and product testing should be applied to ensure process consistency and comparability of the products.

3.3. To what level should the active substance and final product be characterized?

In the example under consideration, it is not possible to make a distinction between the active substance (drug substance) and the finished product (drug product). Therefore, it is not necessary to provide for drug substance characterization or drug substance release testing. The characterization should be performed at the drug product level instead.

Critical parameters ensuring the product's identity, potency and purity should be defined. In this example, as the process does not include substantial manipulation, the amount of individual cell populations and their dependence on different aspects such as patient's health status, age, gender, etc. should be explained.

Distinction between cell type(s) responsible for the desired clinical effect and cell types considered as impurities should be made. Cellular populations should be characterized regarding their potential influence on safety and efficacy. Possible negative impacts on the intended therapeutic use, application route etc. should be identified and tested at release with clinically qualified acceptance limits.

Measurement of total cell number and viability is obligatory. In addition measurement of cell surface markers is expected to be used to monitor identity and purity. A potency assay controlling the functionality of the product should be established for characterization and comparability purposes. This assay also serves as a reference to verify that additional potency assays based on surrogate markers are suitable for their intended use. The surrogate assay can be used for release (see 3.4).

The impurity profile of the product should be known. Product related impurities such as non-viable cells should also be evaluated in the characterization testing.

3.4. What are the specifications of the drug product required to control the quality of the product?

Parameters that are relevant and justified to prove quality of the final product batches, such as relevant surface markers and viability (see 3.3 above) must be included in the drug product specifications. Potency testing based on the functioning of the cells is not expected as a release test for the product.

The strategy for testing including the possibility that the product will be applied before all test results are available and the strategy to ensure sterility should be discussed and justified in the MAA. In the

example, the release testing of the drug product may need to be adapted due to the short shelf life and the limited product availability. Alternatives to classical sterility test (according Ph. Eur. 2.6.1) may be considered. In the eventuality that the results of sterility testing are not available at the time of release, a procedure for risk mitigation should be in place when out-of-specification positive tests results are obtained.

Information on primary packaging materials and excipients is expected.

3.5. What are the requirements concerning analytical tools used for drug product testing?

The assays that account for the release of the final product have to be validated. A full package of information regarding the description and validation of the analytical methods is required for non-compendial methods. Requirements on analytical methods are not ATMP specific. If possible, relevant specific monographs or general texts from the Ph. Eur. can be followed (for example: 2.6.27 Microbiological Control Of Cellular Products; 5.1.6 Alternative Methods for Control of Microbiological Quality; 2.7.24 Flow Cytometry; 2.7.28 Colony-forming Cell Assay; 2.7.29 Nucleated Cell Count and Viability).

3.6. Should the stability of the drug product be studied?

Due to the continuous manufacturing process, there is no drug substance storage and therefore the stability study should be performed on the drug product.

As this product is intended to be used without freezing or storage steps, standard stability studies are not required. However, it is important to study the stability under the defined transport conditions (from the GMP facility to the hospital) and the in-use stability (i.e. what is the maximum time for use). The stability testing strategy should be defined and justified.

The release tests that are stability-indicating should form the panel of analytical methods used in the stability investigation. Results for a sufficient number of batches, manufactured and tested in accordance with the conditions specified in the MAA should be provided.

4. Non-Clinical Studies

4.1. What type of non-clinical development is expected for this product?

In the example under consideration, the therapeutic effect depends on the cell composition, cell number, viability, as well as administration route and the environment to which the product is applied. Applying the risk-based approach it can be concluded that the non-clinical development should be mainly focused to inform on the behaviour of the cell-based product in the altered environment as well as on safety aspects related to the administration procedure.

4.2. What type of pharmacodynamic studies is required?

In vivo studies should be conducted in relevant animal models to elucidate the mode of action of the CD34+ cells in the myocardium. The *in vivo* studies will be supported *by in vitro* studies, showing for example migratory capacity and/or secretion of proangiogenic factors (potency/biological activity, see section 3.3)

The Proof of Concept (PoC) studies can be performed in small animals such as rodents with induced coronary occlusion.

Stand-alone dose finding studies would not be necessary in this example; however, the doses used in these animal studies should be adequate to show a biological activity that is relevant for the therapeutic effect in the intended human use and to support the selection of an effective starting dose for clinical use.

4.3. Which type of pharmacokinetic studies is required to characterise biodistribution, migration and persistence?

In the example under consideration, in view of the short-term non-permanent cell persistence (and according to available relevant scientific information), the risk of unwanted biodistribution is considered limited.

Conventional stand-alone biodistribution studies may be omitted in this context. Information on the behaviour of the cells in the myocardium, i.e. the altered environment, their biodistribution, migration and persistence as well as the effect of the cell numbers applied can be derived from the *in vivo* PoC studies. Taken together, this information is expected to support the proposed mode of action in the target population.

4.4. What type of toxicity studies is expected?

The non-substantially manipulated cells are by themselves not expected to cause toxicity. Yet, the CD34+ cells are administered to a different physiological environment and in non-physiological doses. While stand-alone toxicity studies (e.g. single dose toxicity, repeat dose toxicity, reprotoxicity, genotoxicity, tumourigenicity) are not needed, information on the safety profile of the cell-based product should be collected in the *in vivo* PoC studies, to support the clinical use.

The feasibility and safety of the clinical administration procedure needs to be ensured, and risks related to the administration of the cells need to be addressed. If the cell-based product is planned to be administered via a standard surgical procedure, no separate *in vivo* studies are required. In case that non-standard surgical procedures or specific administration devices are to be used, the associated risks need to be evaluated in suitable *in vivo* studies. Due to the anatomical limitations of small animals, large animal studies are recommended. Using the RBA concept, these studies may be limited or waived if adequate information from published scientific literature is available.

5. Clinical Studies

5.1. What type of clinical development is expected for this product?

Exploratory and confirmatory studies are expected in the MAA to evaluate the efficacy and safety of the CD34+ cell-based product.

In the exploratory studies, endpoints reflecting improvement in cardiac function and structure are acceptable such as left ventricular ejection fraction (LVEF) and wall thickness.

The objective of confirmatory studies is to prove the efficacy in patients with myocardial infarction and to confirm the safety profile.

Applying the risk-based approach it can be concluded that the risks for tumourigenicity, unwanted tissue distribution, unwanted immunogenicity and disease transmission are limited or negligible. However, there is risk of treatment failure / lack of efficacy as well as risk related to the administration procedure.

5.2. Are dose-finding studies required?

The selection of dose to be applied to the patient post myocardial infarction as well as the timing of administration should be justified. The justification and rationale might be based on the combined information from quality, non-clinical data, clinical experience and scientific literature.

5.3. Are pharmacodynamics studies required?

Pharmacodynamic studies should be conducted to provide information on improvement in cardiac structure and function.

It is recommended to generate these data in early (exploratory) clinical studies, as they contribute to estimate the risk of treatment failure or lack of efficacy further on in development.

5.4. Are pharmacokinetic data on biodistribution, persistency and migration required?

In the example under consideration, the risks related to unwanted biodistribution and migration are limited due to short-term persistence of the cells (see non-clinical section) and this justifies the omission of human pharmacokinetic studies.

5.5. How should the safety of the product and the administration procedure be explored?

The autologous, non-manipulated cells are not expected to cause toxicity per se. Toxic effects and safety issues might be caused by e.g. too high doses administered, by issues related to contamination, immune reaction to excipients and residuals, and by safety issues related to the administration procedure.

Risks and complications associated with the product administration, procedure and device should be further assessed in clinical studies, based on already available information from non-clinical studies. In addition, guidance and training should be provided to the clinical sites and health care professionals with regard to the specificities of intracoronary injection of the cell-based product, intending to standardize the administration procedure and to reduce the impact of administration procedure on the efficacy and safety outcome. The same principles apply if the example product is administered in the frame of coronary artery bypass surgery.

Expected procedure and product-related adverse events should be described and appropriately monitored.

5.6. Is there any specific requirements concerning the administration device?

As outlined above the appropriate delivery of the cells is a key factor for a successful treatment. In addition to considerations outlined in the previous section the administration device and technical equipment should comply with the Medical Device Legislation.

5.7. Which studies should be conducted to prove efficacy?

Several factors have been identified that may in combination increase the risk of treatment failure, and thus reduce the chance that the product can be shown to be efficacious for patients with myocardial infarction.

The efficacy of the product should be explored in double-blind, randomized controlled trials, and based on primary outcome measures that are commonly applied in the indication, like all-cause mortality, and recurrent hospitalizations for ischemia or cardiac failures. If deviations for the pivotal trial are proposed, a strong justification will be required.