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The Risk-based approach for ATMP

- Introduction
- Risks & Risk factors
- Methodology Risk profiling
- Ficitious Examples for TEP, CT, GT
- Consequences for MAA dossier

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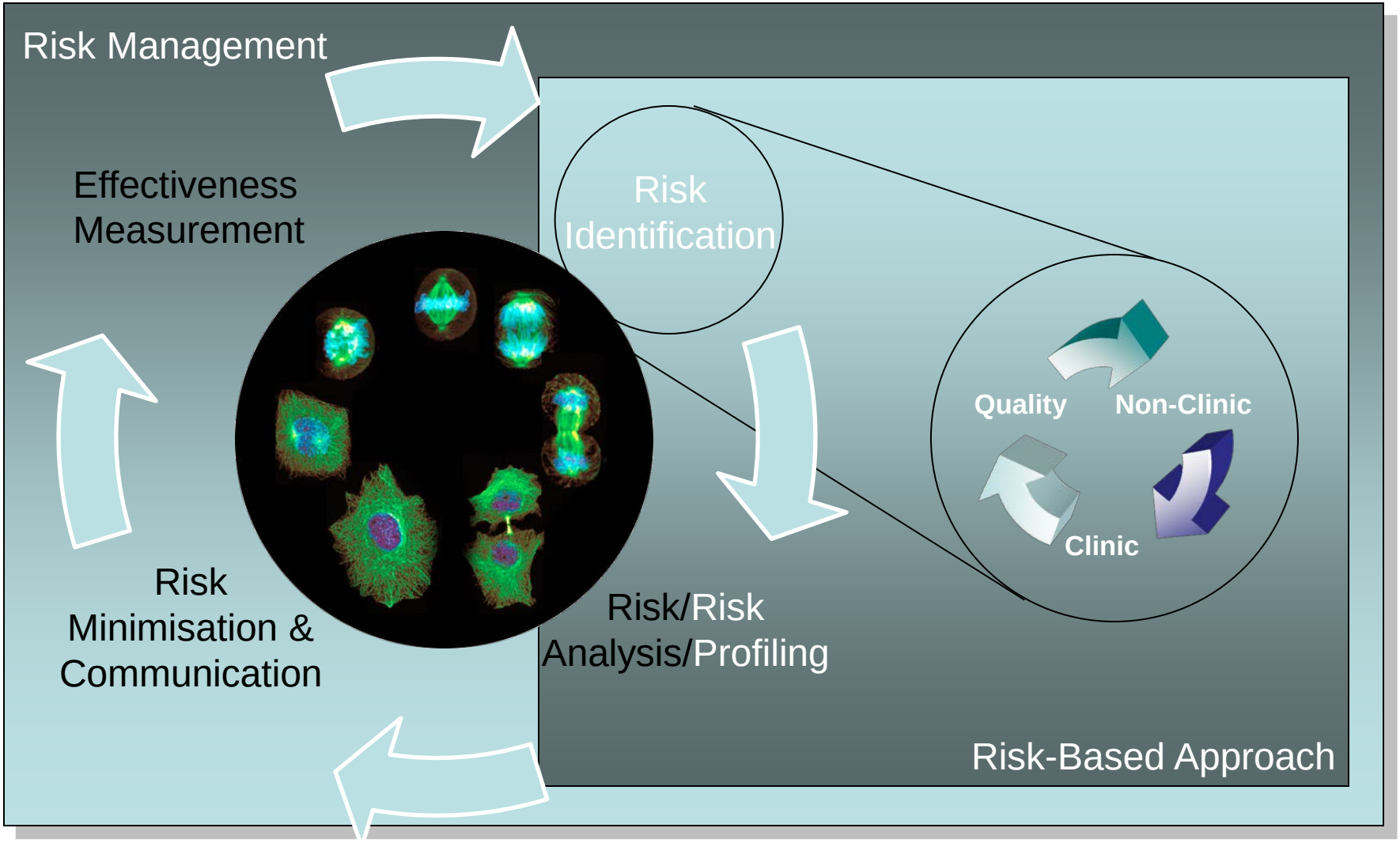
1. Introduction

- GL describes the intention of the RBA and details its methodological application.
- Methodology is based on the identification of risks and associated risk factors of an ATMP and the establishment of a specific profile for each risk.
- With the use of the identified risk profile the Applicant should justify the extent of data presented in the various sections of the MAA dossier.

1. Introduction

- Is not a Risk analysis such as used for Medical devices
- In general, is not an analytical process
- Does not provide a rigid classification system of different risks of a product as whole (e.g. high-risk product *vs.* low-risk product)
- Should be distinguished from Benefit/Risk Assessment, Environment Risk Assessment, quality risk management and Risk Management in the context of MAA evaluation
- Should provide regulatory flexibility


Risk Management
Risk Identification
Risk/Risk Analysis/Profiling
Quality
Non-Clinic
Clinic
Risk-Based Approach
Risk Minimisation & Communication
Effectiveness Measurement

4.1. Risk

- Definition adapted from benefit-risk methodology project (see EMA 549682/2010)
- Any potential “unfavourable effect attributed to the clinical use of ATMP and of concern to the patient and/or to other populations” (e.g. caregivers and off-spring)

Examples of Risks regarding ATMPs

- unwanted immunogenicity,
- tumour formation,
- treatment failure,
- unwanted tissue formation,
- inadvertent germ line transduction,
- toxicity due to degradation/leaching of toxic compounds from structural components, due to unintended alteration of cell homeostasis, due to unwanted targeting of cells/organs, and due to deregulated therapeutic gene expression.

4.2. Risk factors

- Defined as “qualitative or quantitative characteristics contributing to a specific risk following handling and/or administration of an ATMP”

Examples of potential risk factors for CBMP

- Origin of cells (autologous vs allogeneic)
- Ability to proliferate and differentiate
- Ability to initiate an immune response (as target or effector)
- Level of cell manipulation (in vitro / ex vivo expansion/activation, genetic manipulation)
- Aspects of manufacturing process including non-cellular components
- Mode of administration (ex vivo perfusion, local, systemic)
- Duration of exposure (short to permanent)
- Disease & Patient related

Examples of potential risk factors for GTMPs

- Potential of the vector for and its extent of chromosomal integration
- Capacity of the vector for latency/reactivation and/or mobilization
- Vector potential for recombination/re-assortment
- Potential of vector for biodistribution to non-target sites
- Expression of the therapeutic/other gene delivered and duration of expression.
- Replication-incompetence or -competence of a vector
- Vector capacity to inadvertently replicate after complementation by a respective wild-type or helper virus.

4.3. Risk profiling

- Defined as “Methodological approach to systematically integrate all available information on risks and risk factors to obtain a profile of each individual risk associated with a specific ATMP”

- 4 step methodology towards risk profiling

4.3. Methodology of Risk Profiling

- *1st step: To identify risks associated with the clinical use of the ATMP*

- *2nd step: To identify product specific risk factors contributing to each identified risk*

4.3. Methodology of Risk Profiling

- *3rd step: To map the relevant data for each identified risk factors against each of the identified risks*

- To evaluate the contribution of each risk factor to an identified risk, relevant source of data regarding each risk factors can be mapped with help of a two-dimensional table.

- Following information should be provided:

  1-scientific description on the relationship;

  2-studies performed to address this relationship;

  3-locations of these studies in the CTD of the application dossier.

4.3. Methodology of Risk Profiling

- *4th step: To conclude on the risk factor – risk relationships*

- Risk factor-risk combinations for which a reasonable relationship has been identified shall be further detailed in respect to

  - 1- causative scientific relationship;
  - 2- overview of studies performed to determine the impact of the identified risk factors on the particular risk. In case such studies have been omitted, a scientifically sound justification shall be provided why quality, non-clinical and/or clinical data are not needed to be presented in the dossier;
  - 3- conclusion if provided scientific data (quality, non-clinical and clinical) and/or published information addressing the individual risk factor-risk combinations are considered adequate and sufficient to support MAA.
  - It is expected that on completion of the profiling of the identified risks/risk factor combinations a specific profile for each risk can be concluded;

4.4. Fictitious examples to illustrate RBA

- Examples of different matrix tables regarding CTMP, TEP and GTMP are provided in the Annex I to this GL to illustrate the methodology of the RBA.

- Fictitious, non-exhaustive examples, intended for illustration purposes and given to serve as a guide only.

- In the matrix tables, blank boxes indicate that based on the current substantial scientific knowledge no reasonable risk factor/risk relationship is existing.

CBMP – 3rd STEP EXAMPLE

Fictitious example: human ES cell-derived cells secreting bioactive substances injected into CNS

Risk / Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Cell starting material	hESC have inherent capability for teratoma formation. Risk addressed in other sections of this table and in CTD 3.2.S.2.3 - Control of Materials	Possible HLA mismatching. Controlled by donor screening and selection. CTD 3.2.R – Regional information.		Information on cell origin not complete. Lack of information on donor and derivation addressed through viral testing. CTD - 3.2.S.2.3 - Control of		
Culture / feeder cells and growth factors	Culture with GFs or hormones to enhance proliferation/trigger differentiation may induce tumour formation. Process related impurities controlled - CTD 3.2.S.2.3 - Control of Materials; 3.2.S.2.5 - Process validation and/or evaluation; 3.2.S.4 - Control of DS.	Possible immune reaction to animal derived materials, feeder cells - impurities controlled in CTD 3.2.S.2.3 - Control of materials; 3.2.S.3.2 - Impurities.				
Cell population, heterogeneity & differentiation potential	Undifferentiated and undesirable lineage commitment cells resulting from non synchronised	Undesirable lineage commitment cells resulting from non synchronised differentiation; immune reaction CTD 3.2.S.2.5 - Process validation and/or evaluation; 3.2.S.4 - Control of DS.	Presence of cells with inappropriate characteristics resulting from non-synchronised differentiation / Undifferentiated and undesirable lineage committed cells CTD 3.2.S.2.5 - Process validation and/or evaluation; 3.2.S.4 - Control of DS (potency assay for DS) CTD - 3.2.S.3 - Characterisation and for DP CTD 3.2.P.5 - Control of DP and CTD 3.2.P.8 - Stability			
		Distribution of cells may increase risk of immunogenicity. Biodistribution study CTD 4.2.2.3 - Pharmacokinetics - Distribution	Potential loss of activity due to loss of cells by migration. Biodistribution study CTD 4.2.2.3 - Pharmacokinetics - Distribution			Biodistribu study. CTI Pharmaco Distributic
			Limitations of used animal model may reduce predictive value of efficacy, POC study -		animal study may not be appropriate for detection of unwanted	

Possible HLA mismatching. Controlled by donor screening and selection.
CTD 3.2.R – Regional information.

Culture with GFs or hormones to enhance proliferation/trigger differentiation may induce tumour formation. Process related impurities controlled - CTD 3.2.S.2.3 - Control of Materials; 3.2.S.2.5 - Process validation and/or evaluation; 3.2.S.4 - Control of AS.

Potential loss of activity due to loss of cells by migration. Biodistribution study CTD 4.2.2.3 - Pharmacokinetics - Distribution

5. Consequences for MAA dossier

- Important for the Applicant to present the RBA to the development of their product in a logical and meaningful way, in order to contribute to the justification of the data package at the time of MAA assessment.

- Results of RBA can be used as one of the starting points for safety specification as part of RMP.

- Adaptive requirements for ATMPs are important to foster their MA.
- The RBA permits flexibility in the data package that is submitted to obtain a marketing authorisation.
- **Can the RBA used as a helpful tool to promote a more frequent appearance of ATMPs for public health?**