Chapter 18

Risk Management

Joaquim Vives and Judit Amposta

Abbreviations

CAR	Chimeric Antigen Receptor
CQA	Critical Quality Attribute
EBMT	European Blood and Marrow Transplantation
EMA	European Medicines Agency
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
FMEA	Failure Mode Effects Analysis
FMECA	Failure Mode, Effects and Criticality Analysis
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard Operability Analysis
HLA	Human Leukocyte Antigen
HSC	Hematopoietic Stem Cells

J. Vives (✉)

Servei de Teràpia Cel·lular, Banc de Sang i Teixits, Edifici Dr. Frederic Duran i Jordà, Barcelona, Spain

Musculoskeletal Tissue Engineering Group, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain
e-mail: jvives@bst.cat

J. Amposta

Freelance Quality Consultant, Mataró, Barcelona, Spain
e-mail: jamposta@bioqualy.cat

© The Author(s) 2021

M. Aljurf et al. (eds.), *Quality Management and Accreditation in Hematopoietic Stem Cell Transplantation and Cellular Therapy*,
https://doi.org/10.1007/978-3-030-64492-5_18

ICH	International Conference on Harmonization
ISCT	International Society for Cell and Gene Therapy
ISO	International Organization for Standardization
JACIE	Joint Accreditation Committee of the ISCT-Europe & EBMT
MSC	Multipotent Mesenchymal Stromal Cells
PHA	Preliminary Hazard Analysis
QbD	Quality by Design
QC	Quality Control
QoL	Quality of Life
RD	Related Donor
RRF	Risk Ranking and Filtering
SOP	Standard Operating Procedures
UD	Unrelated Donor
US	United States

Defining Risk in Cell Therapy

A risk is defined as a combination of the probability of occurrence of harm and the severity of that harm [1]. It is recognised that complex processes are involved in cell therapy embracing a life cycle that encompasses people, facilities and equipment, reagents and materials, documents, and procedures. The risk of altering any critical quality factors related to safety (that is, for any of the stakeholders involved) and efficacy of the cell-based product administered to patients need to be taken into consideration in order to improve established workflows and pursue better therapies. In our context, major risks to be considered are those affecting the health of donors and patients, so all efforts should focus on the identification of risks that may critically impact on their health and the cost of cell processing to make improved therapies affordable. Fortunately, existing pharmaceutical standards, such as GxP (Good Scientific Practices, where “x” stands for the following: M, manufacturing; L, laboratory; T, tissue; D, distribution; C, clinical; PV, pharmacovigilance), already developed tools for risk management that can cover not only the critical quality attributes (CQA) of the cellular products but all the activities involved in the entire process, from the procurement of starting material from donors to the administration in patients and their follow-up, that is “from vein (of donor) to vein (of patient)” [2–4].

The advent of a new generation of cell-based medicines, in which cells are substantially manipulated, even genetically (e.g. MSC, CAR-T cells, iPSC), poses major risks and therefore robust methods need to be established and validated to ensure safety consistently [2, 5–7].

The Foundation for the Accreditation of Cellular Therapy (FACT) and Joint Accreditation Committee of the International Society for Cell and Gene Therapy (ISCT)-Europe & European Society for Blood and Marrow transplantation (EBMT)

(JACIE) have published guidelines that incorporate risk-based assessment as a key element to consider in every critical decision [8]. However, it is important to note that the acknowledgement of risks does not make an unsafe or a low-quality product into a safer one. In other words, risk assessment is useless unless a proactive attitude and willingness to make a (positive) difference exist. This means that risk management is not adding an additional documentation burden but a critical quality tool that holds the potential to assist us to better understand the weakest points of processes involved in the life cycle of cell therapy treatments. Then, improvements can be implemented upon accurate documentation of processes, analysis of risks, and definition of suitable actions for mitigation. Several other factors must be taken into consideration, ranging from the design of facilities and the manufacturing process to adequate personnel training and efficient documentation system, to name a few [3]. The main goal of following a risk-based approach is to improve decision-making and lead to a more effective and efficient management and oversight framework, as well as optimal use of institutional resources.

Quality risk management (QRM) is a tool recognised and incorporated in mandatory and voluntary accreditation schemes, GMP being the strictest standard in this regard [8]. GMP is of mandatory application in drug manufacturing and, therefore, they are also applied to substantially manipulated cell-based products, which are considered medicines by most regulatory authorities [6, 9]. QRM is in fact the adaptation of the topic Q9 from the guidelines issued by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. This is the major guideline providing principles and examples of tools for QRM that can be applied to different aspects of pharmaceutical quality. Importantly, ICH Q9 provides advice on the use of QRM considering that the level of effort and formality must be in accordance with the level of risk [1].

Guideline ICH Q10 (on the pharmaceutical quality system) establishes the structure to build an effective pharmaceutical quality system to support pharmaceutical development and manufacturing across the product life cycle incorporating QRM as a facilitator agent. Here it is important to note that the earlier we start considering risks, the better the management of processes could be expected in the future and, subsequently, this would lead to safer treatments. Likewise, voluntary accreditation schemes (e.g. FACT-JACIE, ISO9001) incorporate QRM, thereby showing some similarities and/or equivalences between standards [8].

The Quality Risk Management Process

In cell therapy, QRM can be defined as the systematic process for risk assessment, risk control, risk review, and communication of the quality risks in the processes involved during the entire life cycle of the treatment. A standardised and robust system is needed to identify risks, determine their potential hazards, and reduce or eliminate those that are unacceptable.

According to current FACT-JACIE guidelines, the identification of a risk can be made by providing a description and establishing the context or scope, so all the possible risks are identified and the possible ramifications or impact in all areas are analysed thoroughly [10]. Once the context or scope has been established successfully, the next step is identification and evaluation of potential risks by either source or effect. During source analysis, the source of risks is analysed and appropriate mitigation measures are put in place. This risk source could be either internal or external to the system. During problem analysis, the effect rather than the cause of the risk is analysed. Once the risk has been identified, it must be assessed on its potential criticality or on their likelihood of occurrence and the potential impact by either quantitative or qualitative evaluation, as shown in Table 18.1 and further described in this section.

There are many different approaches to calculating risk, and there are tools that can help assist in defining the probability of the effect occurring, the root cause, effects, and magnitude of risk under different scenarios. Risk Evaluation and Mitigation Strategies (REMS, in the USA) or Risk Management Plan (RMP, in the EU) may include (but are not limited to) detailed procedures for providing education and instructions to personnel involved (including donor and patients), monitoring patients, managing adverse events, and reporting outcomes to manufacturers. Once the risk assessment is established, an RMP can be developed and implemented. It comprises the effective controls for mitigation of risk. Risk management involves the justification and rationale for accepting risks and how to manage their impact if applicable. This can often be established in a simple one-page document for change with low impact and risk.

The QRM must be integrated into the pharmaceutical quality system to be properly documented and become a consistent tool for improvement. Risk management must be proactive rather than reactive, and it must be incorporated into the culture of prevention of the organisation. One could say that the process of QRM takes the steps depicted in Fig. 18.1, which are taken from current GMP [11] and further discussed next.

Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. Quality risk assessment begins with a well-defined problem description or risk question. In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. The document reflecting the risk assessment can be completed by following three successive steps, as described next.

Step 1: Risk identification The purpose of this phase is to recognize and record the risks of the situation being evaluated, identifying the origin of the risks and their causes. It aims to answer the question: What could go wrong? Risk identification

Table 18.1 Methods commonly used for identification of risks

Method	Objectives	Pros	Cons
FMEA	FMEA identifies, analyses, and prevents potential failures, as well as their effects and causes	Method widely used in different sectors If used prospectively, it may highlight shortcomings that had not been previously contemplated It is more objective than other tools if severity, probability, and detectability are categorised precisely	Not useful for very complex processes. If this were the case, specific steps should be selected
FMECA	FMECA takes FMEA process one step further. Each failure mode is assigned a severity level	The FMECA team will not only identify but also investigate potential failure modes and their causes being able to prioritise their importance	Not useful for very complex processes. If this were the case, specific steps should be selected
FTA	FTA identifies the possible root causes of a failure or unwanted consequences, to prevent recurrence The results of the analysis are represented pictographically in the form of a fault mode tree using symbols and standards	Visual method Useful for complex systems If applied in the design phase, it provides an overview of the risks that can help to create requirements, before starting the process	Limited approach as it only evaluates one unwanted event for each tree
HACCP	HACCP is a preventive safety system in which every step in the manufacture, storage, and distribution of a food product is scientifically analysed for microbiological, physical, and chemical hazards	Determines critical control points in the process Allows continuous improvement and better knowledge of the processes	So far it is a tool mainly used in the food sector with great potential for application in cell therapy. It should be reviewed frequently to introduce all the changes being made in the process
HAZOP	HAZOP is a technique for identifying risks that occur as a result of a deviation of the process variables, with respect to the operating parameters of the system	Helps to identify potential deviations from normal use or design intentions The output analysis is a list of critical operations for risk management	Qualitative tool
PHA	PHA is based on applying prior experience or knowledge of a hazard or failure to identify future hazards that might cause harm and to estimate their probability of occurrence	It is most used early in the development of a project when there is little information on design details or operating procedures Simple method, easy to implement	It is only a preliminary estimate of the risks of the system. Hazards identified will require further assessment with other risk management tools
RRF	RRF is a tool for comparing and ranking risks	It is particularly helpful in situations in which the possible risks and the consequences to be managed are diverse	Good justification of filtering must be made to ensure its relevance

FMEA failure mode effects analysis, *FMECA* failure mode, effects and criticality analysis, *FTA* fault tree analysis, *HACCP* hazard analysis and critical control points, *HAZOP* hazard operability analysis, *PHA* preliminary hazard analysis, *RRF* risk ranking and filtering

methods that may be used include reviewing of historical data, brainstorming, elementary cause, and assign consequences (e.g. fishbone Ishikawa, diagram, failure mode/effect table), fault tree analysis, process map, flow charts, just to name a few.

Step 2: Risk analysis Estimation of the risk associated with the identified hazards can be either a qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (aka. detectability) also contributes to the ability to estimate risk. Risk analysis aims to answer the following questions: What are the chances (probability) of happening? What would be the consequences?

There are several methods suitable for the management of risks. From these, the next seven recognised tools are considered relevant in the cell therapy field (further described in Table 18.1).

- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk Ranking and Filtering (RRF)

Depending on the particular situation to be evaluated, one method or the other will be chosen. When the risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as “high”, “medium”, or “low”, which should be defined in as much detail as possible. The application of statistical tools (e.g. Pareto charts, histograms, Process Capability Index – CpK, dispersion graphs) together with these risk management tools helps to obtain additional information.

Step 3: Risk evaluation The purpose of this final step is to compare the identified and analysed risk(s) against given risk criteria.

Risk Control

Risk control involves the decision-making of either (A) reducing the risk or (B) accepting and managing the residual risk. Ideally, identified risks will be reduced to acceptable levels, always remembering the premise that the effort and resources applied must be proportional to the risk. It aims to answer the following questions: Is the risk beyond the acceptance level? What can I do to eliminate or reduce the risk? What is the appropriate balance among benefits, risks, and resources? Are there any new risks introduced because of the actions taken to control a risk?

Fig. 18.1 Overview of quality risk management along the life cycle of cell therapies

Step 1: Risk reduction Here we must focus on actions to decrease severity and the likelihood of any harm occurring when it exceeds a specified (acceptable) level (Fig. 18.1). This step may imply a redesignation of the process (e.g. inadequate controls, lack of robustness of the process).

Step 2: Risk acceptance Risk acceptance is a decision to accept risk after the evaluation of severity, likelihood, and the detectability of hazards. Risk acceptance can be a formal decision to accept the residual risk (risks well specified) or it can be a passive decision in which residual risks are not specified (risks are part of the natural variability of the process). For some types of harms, even the best-quality risk management practices may not help to eliminate the risk completely, but only reduce it partially. This (specified) acceptable level may depend on many parameters and should be decided on a case-by-case basis. The rationale behind such a strategy should be documented, residual risk described, and appropriate management strategies put in place.

Risk Review

It is very important to carry out continuous monitoring and verification of risk management to identify changes in the assessed situation. This could generate new risks or affect the effectiveness of the initial risk management plan. We must be aware that the probability of risk and the risks themselves will change when the conditions change. Risk review serves as a verification and is key to promote the concept of continuous improvement. Risk review is easier to perform if there is someone in charge of monitoring the progress of the implementation of the action plan . Importantly, this step adds value to the risk analysis management.

Risk Communication

Risk communication is the act of sharing information on risk and risk management between the decision makers and stakeholders involved in critical steps of the cell therapy process (as discussed in section “[Stakeholders Involved in Risk Management](#)”), thus ensuring an effective information flow. Parties can communicate at any stage of the risk management process (dashed arrows in Fig. 18.1). The output of the quality risk management process should be appropriately communicated and documented (solid arrows in Fig. 18.1). The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability, or other aspects of risks to quality. Communication need not be carried out for every risk acceptance. Risks which are subject to frequent changes by trend need to be reported more frequently than constant risks.

Stakeholders Involved in Risk Management

Activities involved in risk management of cell therapy processes should be carried out by multidisciplinary teams, including experts in the different areas (e.g. quality assurance, process and quality control, medical management, pharmacy) and a risk management coordinator. It is very important to establish well-defined, up-to-date standard operating procedures (SOP) and having the necessary resources. This team should meet on a regular basis to keep the risk analysis in a living state, which is updated with the latest data available (e.g. incidences, non-conformities, bio-vigilance).

Illustrative Examples of Specific Applications

Risks in cell therapy are diverse due to the complexity of the whole process and may impact on any critical step along the life cycle. A good understanding of the six Ws (summarised in Box 18.1) is key to realise the potential of risk management. Some explanatory examples are described next to illustrate the applicability of QRM and its potential to support continual improvement.

Box 18.1 The Six W of Risk Management in Cell Therapy

- *Why?* Improve safety of donors; improve survival and QoL of patients
- *What?* Identify hazards and the risk of impacting in critical steps along the life cycle of cell therapies
- *Who?* Multidisciplinary team involving quality assurance, process and quality control, medical management
- *Where?* Hospitals and processing units
- *When?* Always, being part of a continual improvement process
- *How?* Following the risk management process

Related vs. Unrelated Donors

Donation of HSC from related donors (RD) is associated with higher occurrence of adverse events (including death) than in unrelated donors (UD) [12]. Circumstances particularly applicable to RD are complex and contribute to increased risk. Risks include the lack of regulatory guidance, logistical and financial barriers, lack of the benefit of anonymity, close relationship with the transplant recipient, and the consequent pressure to donate. RD tend to be older than UD and therefore more likely to have morbidities. The impact of quality management in driving change was confirmed by Anthias and collaborators, who reported that improvements observed in donor care were successfully achieved in areas where recent FACT-JACIE standards were introduced [12]. Continual improvement can be further achieved by gradual understanding of risks, particularly present in each individual institution.

Processing of Cell Therapy Products

Cell-based therapies are rapidly evolving from traditional HSCT to current genetically engineered immune cells and mesenchymal stem cells [13, 14]. Therapeutic activity of cell-based products is susceptible to intrinsic biological variability, as opposed to traditional pharmaceutical drugs, such as small molecules or biologicals. In this context, it is crucial to deeply understand the cell's critical quality attributes (CQA) (directly impacting on the product's safety profile and clinical efficacy) and how these are affected by any disturbance in the process [15]. Moreover, cell manufacturing is a poorly automated process, prone to operator-introduced variations, and affected by heterogeneity of the processed organs and tissues and batch-dependent variability of reagent efficiency [16]. In a recent study, we reported the impact of risks associated with main failure groups (that is process, equipment, personnel, documentation, environment, reagents, and materials) on the specifications of a mesenchymal cell-based product with multiple applications including the management of acute graft-versus-host disease (GvHD) [17]. From all risks that were identified, those associated to cell processing and apparatus were high in the initial steps of product manufacturing but replaced by risks associated to operator errors at later stages of production. In this study, the risk analysis was performed following FMEA/FMECA and actions were prioritised using a simple Pareto chart, proving to be a powerful method within a clinical cell therapy manufacturing context, as well as an ideal vector for prompting alternative and proactive improvement processes [18, 19]. Moreover, the intrinsic flexibility of the method makes it ideal for critical risk assessment in all processes related to the entire life cycle of the cell-based product, thus allowing to properly identify risk priorities and corresponding control activities, supports the identification of necessary actions for quality improvement, and provides a specific model for guidance of cell transplantation centres and cell processing facilities approaching risk management for the first time, especially if lacking personnel with specific risk analysis expertise [16, 18, 19].

Patients

From EBMT registry data, Snowden and collaborators confirmed the correlation of occurrence of new centre accreditation with improvements in patient survival and reduction of procedural mortality, demonstrating the clinical benefits of adoption of quality standards [20]. Consistently, transplant centres in advanced phases of FACT-JACIE accreditation are linked to significantly higher survival rates, independent of year of transplantation or other risk factors [21]. Therefore, the implementation of FACT-JACIE standards contribute to improved processes and mitigate existing (maybe hidden) risks. In addition to general QRM, specific tools have been created as is the case of the EBMT risk score, providing a simple way to assess benefits and risks of HSCT for an individual patient pre-transplant, by assessing only five factors (namely, age of the patient, stage of the disease, time interval from diagnosis to transplant, HLA matching, and gender of donor and recipient). Higher risks are observed for an individual patient with increasing score from 0 (best) to 7 (worst) in an additive way [22]. Integration of the EBMT risk profile into the risk assessment should guide in the decision process, ultimately leading to a better decision in the selection of transplant patients.

Final Remarks

Remarkable improvements can be achieved by following simple risk assessment tools. Growing evidence shows that the systematic and comprehensive evaluation of risks impacting on safety and efficacy of cell therapy contributes to proper management of risk affecting donors and patients. Institutions already accredited for standards incorporating QRM are best positioned to drive change in cell therapy by a systematic risk-based approach. Rather than following each of the different quality guidelines and standards separately, we encourage institutions to customise their own methodology of QRM to fit them into the unique characteristics and needs of their institutions. Importantly, quality management systems need to be flexible enough for continuous evolution from traditional HSCT and stay open to the future trends in cell and gene therapy.

It should be noted that Lean Six Sigma strategies are fully compatible with QRM. In fact, some hospitals and blood and tissue banks are already using these tools and we expect this to become the trend if they both are dynamic and facilitate continual improvement in the life cycle of the treatment.

References

1. European Medicines Agency. ICH guideline Q9 on quality risk management. London; 2015.
2. Mount NM, Ward SJ, Kefalas P, Hyllner J. Cell-based therapy technology classifications and translational challenges. *Philos Trans R Soc Lond Ser B Biol Sci.* 2015;370(1680):20150017.

3. Vives J, Carmona G, Vives J, Carmona G. Guide to cell therapy GxP. 1st ed: Academic Press (Elsevier); 2015. 266 p.
4. Trias E, Lomas R, Tabera J, Piteira AR, Tilleman K, Casaroli-Marano RP, et al. EuroGTP II: a tool to assess risk, safety and efficacy of substances of human origin. *Int J Qual Health Care*. 2019;
5. Galipeau J, Sensébé L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. *Cell Stem Cell*. 2018;22(6):824–33.
6. Schneider CK, Salmikangas P, Jilma B, Flamion B, Todorova LR, Paphitou A, et al. Challenges with advanced therapy medicinal products and how to meet them. *Nat Rev Drug Discov*. 2010;9(3):195–201.
7. Fischbach MA, Bluestone JA, Lim WA. Cell-based therapeutics: the next pillar of medicine. *Sci Transl Med*. 2013;5(179):179ps7.
8. Oliver-Vila I, van Deusen A, Palau R, Vives J. Quality compliance in the development of cell-based medicines in non-pharma environments. *BMC Proc*. 2015;9(Suppl 9):P29.
9. Oberweis CV, Marchal JA, López-Ruiz E, Gálvez-Martín P. A worldwide overview of regulatory frameworks for tissue-based products. *Tissue Eng Part B Rev*. 2020;26(2)
10. FACT-JACIE. Guidance to accompany the FACT-JACIE international standards for hematopoietic cellular therapy product collection, processing, and administration, Seventh Edition. Barcelona, Spain; 2018.
11. Commission E. EudraLex. The rules governing medicinal products in the European Union. Volume 4. Good Manufacturing Practice. Guidelines on good manufacturing practice specific to advanced therapy medicinal products. Brussels; 2017.
12. Anthias C, O'Donnell PV, Kiefer DM, Yared J, Norkin M, Anderlini P, et al. European Group for Blood and Marrow Transplantation Centers with FACT-JACIE accreditation have significantly better compliance with related donor care standards. *Biol Blood Marrow Transplant*. 2016;22(3):514–9.
13. Vives J, Mirabel C. Multipotent mesenchymal stromal cells from bone marrow for current and potential clinical applications. In: Reis RL, editor. *Encyclopedia of tissue engineering and regenerative medicine*. Oxford: Academic Press; 2019. p. 503–12.
14. June CH, Sadelain M. Chimeric antigen receptor therapy. *N Engl J Med*. 2018;379(1):64–73.
15. García-Fernández C, López-Fernández A, Borrós S, Lecina M, Vives J. Strategies for large-scale expansion of clinical-grade human multipotent mesenchymal stromal cells. *Biochem Eng J*. 2020;159:107601.
16. Lopez F, Di Bartolo C, Piazza T, Passannanti A, Gerlach JC, Gridelli B, et al. A quality risk management model approach for cell therapy manufacturing. *Risk Anal*. 2010;30(12):1857–71.
17. Grau-Vorster M, Rodríguez L, Del Mazo-Barbara A, Mirabel C, Blanco M, Codinach M, et al. Compliance with good manufacturing practice in the assessment of immunomodulation potential of clinical grade multipotent mesenchymal stromal cells derived from Wharton's Jelly. *Cells*. 2019;8(5)
18. Del Mazo-Barbara A, Nieto V, Mirabel C, Reyes B, García-López J, Oliver-Vila I, et al. Streamlining the qualification of computerized systems in GxP-compliant academic cell therapy facilities. *Cytotherapy*. 2016;18(9):1237–9.
19. Del Mazo-Barbara A, Mirabel C, Nieto V, Reyes B, García-López J, Oliver-Vila I, et al. Qualification of computerized monitoring systems in a cell therapy facility compliant with the good manufacturing practices. *Regen Med*. 2016;11(6):521–8.
20. Gratwohl A, Brand R, McGrath E, van Biezen A, Sureda A, Ljungman P, et al. Use of the quality management system “JACIE” and outcome after hematopoietic stem cell transplantation. *Haematologica*. 2014;99(5):908–15.
21. Gratwohl A, Brand R, Niederwieser D, Baldomero H, Chabannon C, Cornelissen J, et al. Introduction of a quality management system and outcome after hematopoietic stem-cell transplantation. *J Clin Oncol*. 2011;29(15):1980–6.
22. Gratwohl A. The EBMT risk score. *Bone Marrow Transplant*. 2012;47(6):749–56.

Open Access This chapter is licensed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license and indicate if changes were made.

The images or other third party material in this chapter are included in the chapter's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the chapter's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder.