that is permissive to infection by amphotropic MLV-like RCR, while VPC containing the gibbon ape leukemia virus envelope should be tested on a human cell line. Other retroviral envelopes should be tested on a cell line permissive for infection by the relevant RCR.

If derivation of VPC includes use of a retroviral vector containing an envelope distinct from the packaging vector, for example, an ecotropic MLV, the potential exists for introduction of an RCR with that envelope. Even though an ecotropic MLV RCR may present a minimal direct safety risk to humans, the presence of any replication-competent genome in the VPC is problematic because of the increased probability of generating an RCR with a human host range by recombination with elements within the VPC.

In those cases where VPC are derived at any step by infection with an ecotropic retroviral vector, testing of the MCB for the presence of ecotropic RCR is recommended. Both cells and supernatants should be tested using a method validated to detect the appropriate positive control (for example: D56 (Ref. 2) or XC (Ref. 10)). Refer to the guidance provided in section III.B. to determine the amount of material for testing.

2. Working Cell Bank Testing (one time testing)

Either supernatant testing or cocultivation of cells for RCR is recommended using conditions described for master cell bank testing.

3. Testing of Retroviral Vector Supernatant Product and End of Production Cells

Both retroviral vector supernatant lots and end of production cells should be tested for RCR as specified in section III.B. This recommendation is based on data and experience reported at the 1997 FDA/National Institutes of Health (NIH) Gene Therapy Conference in which RCR in vector production lots was not consistently detected by both assays, or one assay to the exclusion of the other. These data support the position that dual testing provides a complementary approach to assuring RCR free retroviral supernatant.

4. Testing of Ex Vivo Transduced Cells

a. Cultured < 4 days after transduction

Data presented at the 1997 FDA/NIH Gene Therapy Conference indicated that for ex vivo transduced cells, a minimum culture period of 4 days from the start of transduction is necessary for amplification and detection of an RCR. As a result, for ex vivo transduced cells cultured for a period less than four days, archiving

of the quantity of product needed to perform RCR testing is recommended in place of active RCR testing. Refer to the guidance in section III.B. to determine the amount of material to be archived. Samples should be archived with appropriate safeguards to ensure long-term storage (e.g., a monitored freezer alarm storage system) and an efficient system for the prompt linkage and retrieval of the stored samples with the medical records of the patient and the production lot records.

b. Cultured $\geq$ 4 days

When ex vivo transduced cells are in culture for a period of time greater than or equal to 4 days from the start of transduction, cells and the appropriate volume of culture supernatant should be tested for RCR. Refer to guidance in section III.B. of this document for determining the amount of material for testing. In situations where ex vivo transduced cells cannot be cryopreserved during testing, and must be administered to patients prior to the availability of testing results, culture assays should be initiated at the time of patient administration. In these situations, alternative methods such as PCR may be appropriate to provide an initial analysis. Any alternative methods should be developed in consultation with CBER. Data on sensitivity, specificity and reproducibility should be provided to support the use of alternative methods.

Table 1. Recommendations for Product Testing

	RCR Testing for Expected RCR[1]		RCR Testing for Ecotropic MLV	
Manufacturing Step	**Cells**	**Supernatant**	**Cells**	**Supernatant**
MCB				
-Derived by infection with Ecotropic MLV vector	**Yes**	**Yes**	**Yes**	**Yes**
-Derived by transfection of retroviral vector plasmid	**Yes**	**Yes**	No	No
WCB	**Yes OR**	**Yes**	No	No
End of Production Cells	**Yes**	NA[2]	No	No
Vector-Containing Supernatant	NA	**Yes**	No	No
Ex vivo Transduced Cells				
-Cultured <4 days after Transduction	No – archive	No – archive	No	No
--Cultured ≥4 days after transduction	**Yes**	**Yes**	No	No

[1] RCR testing should be based on the type of packaging cell line used to derive the VPC. Consult text in section III.A.1. of this document for details.
[2] NA, not applicable.

B. Amounts for Testing

1. Supernatant Testing

In all cases, it would be appropriate to test at least 5% of the total supernatant by amplification on a permissive cell line. However, for instances where supernatant production volumes are greater than 6 liters, and therefore, testing of 5% may not always be practical, an alternative approach is described below. In order to utilize the alternative approach, the largest volume where a single infectious RCR can be detected should first be determined. When high titer retroviral vector preparations are used, interference in RCR detection may occur. In such cases, detection of a single RCR may require use of such small volumes in each test that the application of this alternative approach may not be practical. Sponsors are encouraged to develop more sensitive detection methods that overcome the interference effect of high titer retroviral vector preparations in order to use the alternative approach.

a. Alternative approach for determining total volume of retroviral vector supernatant to be tested

A statistical approach has been applied to the determination of the total volume of retroviral supernatant to be tested for RCR. This calculation is independent of production lot size and is based on the application of the Poisson distribution. It is recommended that sufficient supernatant be tested to ensure a 95% probability of detection of RCR if present at a concentration of 1 RCR/100 ml. At this concentration, a volume of about 300 ml will have a 95% probability of containing an RCR. Therefore, assuming the assay is sensitive enough to detect a single RCR, a test volume of 300 ml will provide 95% probability of detecting RCR. A more detailed explanation of the rationale and the mathematical formulas applied is found in Appendix 1-1.

To support the underlying assumption that a single retrovirus will be detected, one must determine a volume in which a single RCR can be detected by an individual RCR assay. Based on the determination of this volume, the total test volume should then be divided into replicate samples, each containing the volume demonstrated to detect a single RCR. An RCR standard has been developed, its infectious titer has been determined, and it is available through the American Type Culture Collection (ATCC). The standard can be used as a reference for determination of the volume in which a single RCR can be determined. Refer to Appendix sections 1-2 and 1-3 for detailed information about the RCR standard and how it can be used to determine the replicate size and number for RCR detection.

b. Assays for supernatant testing

Supernatant assays should include culture of supernatant on a permissive cell line (ex. *Mus dunni* for amphotropic MLV (Ref. 5)) for a minimum of *5* passages in order to amplify any potential RCR present. The amplified material may then be detected in an appropriate indicator cell assay (e.g., PG-4 S^+L^- (1)). All assays should include relevant positive and negative controls to assess specificity, sensitivity and reproducibility of the detection method employed. Each lot of retroviral vector supernatant should be tested for inhibitory effects on detection of RCR by using positive control samples that are diluted in vector supernatant.

2. Cell Testing

The current recommendation to test 1% of the total cells or 10^8 (whichever is less) pooled vector-producing cells or ex vivo transduced cells by co-culture with a permissive cell line will remain in place. Public consensus expressed at the 1996 and 1997 FDA/NIH Gene Therapy Conferences was in support of the current recommendations for cell testing, in light of the variety of vector producing cells and vector backbones used, and the difficulty that is presented in development of a standard RCR producing positive cell stock.

Co-culture assays should include culture with a permissive cell line (ex. *Mus dunni* for amphotropic MLV (Ref. 5)) for a minimum of five passages in order to amplify any potential RCR present. The amplified material may then be detected in an appropriate indicator cell assay (e.g., PG-4 S+L- (1)). All assays should include relevant positive and negative controls to assess specificity, sensitivity and reproducibility of the detection method employed.

IV. RECOMMENDATIONS FOR PATIENT MONITORING

Active monitoring for evidence of RCR infection in patients enrolled in gene therapy clinical trials using retroviral vectors is currently recommended in a letter to Sponsors of INDs Using Retroviral Vectors, dated September 20, 1993. Based on input from the gene therapy community, problematic aspects of the current recommendations were defined as the number of time points for testing, the recommendations for life-long annual testing, and the types of assays recommended.

A. Testing Schedule

Note: This section IV.A. immediately below has been supplemented by the "Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events." [2]

This guidance presents alternatives to the time points for monitoring originally described in a letter to Sponsors of INDs Using Retroviral Vectors, dated September 20, 1993. These recommendations are based on data accumulated in on-going gene therapy clinical trials using retroviral vectors (Refs. 6, 7). The monitoring schedule recommended here should include analysis of patient samples at the following time points: pre-treatment, 3 months, 6 months, 1 year after treatment, and yearly thereafter. If all post-treatment assays are negative during the first year, the yearly samples should be archived. Samples should be archived with appropriate safeguards to ensure long-term storage (e.g., a monitored freezer alarm storage system) and an efficient system for the prompt linkage and retrieval of the stored samples with the medical records of the patient and the production lot records.

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[2] See http://www.fda.gov/cber/genetherapy/gtpubs.htm.

If any post-treatment samples are positive, further analysis of the RCR and more extensive patient follow-up should be undertaken, in consultation with CBER. It is further recommended at the time of collection of the yearly patient specimen, that a brief clinical history should be obtained. This history should be targeted towards determination of clinical outcomes suggestive of retroviral disease, such as cancer, neurologic disorders, or other hematologic disorders. Suspect clinical outcomes may trigger additional analysis of archived samples, in consultation with CBER. If patients die or develop neoplasms during a gene therapy trial, every effort should be made to assay for RCR in a biopsy sample of the neoplastic tissue or the pertinent autopsy tissue.

B. Recommended Assays

Two methods are currently in use and recommended for detecting evidence of RCR infection in patients: 1) detection of RCR-specific antibodies; and 2) analysis of patient peripheral blood mononuclear cells by polymerase chain reaction (PCR) for RCR-specific DNA sequences. The choice of assay may depend on the mode of vector administration and the clinical indication. For example, it has been shown that direct administration of VPC or repeat direct injection of a vector can result in vector-specific antibodies which do not correlate with the presence of RCR (Refs. 6, 7). Therefore, in cases where vector or vector-producing cells are directly administered, a PCR assay may be preferable over serologic monitoring. Additional instances where monitoring of patients by PCR may be preferred over serologic monitoring, are those cases where the patients are immunocompromised to an extent that antibody production may be minimal or not at all. In either situation, all positive results should be pursued by direct culture assay to obtain and characterize the infectious viral isolate.

V. DOCUMENTATION OF RCR TESTING RESULTS

RCR testing results from production lots and patient monitoring should be documented in an amendment to the investigational new drug (IND). Positive results from patient monitoring should be reported immediately as an adverse experience in the form of an IND safety report (21 CFR 312.32). Negative results should be reported by way of the IND annual report (21 CFR 312.33). In addition, CBER encourages members of the gene therapy community to publish data and/or provide permission in the IND for FDA to discuss data publicly in order to enhance the cumulative data base on RCR testing assays, experience with different vector producer cell lines, patient monitoring and safety.

VI. CONCLUSION

This guidance provides additional guidance for testing for RCR associated with the use of gene therapy retroviral vectors. These supplemental recommendations are based on data and analyses generated by CBER and by members of the gene therapy community. For safety testing of retroviral vectors or vector-transduced cells, IND sponsors may either follow the

recommendations previously provided in the "Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy," or follow the recommendations outlined here. Application of this supplemental guidance: 1) effectively reduces the volume of supernatant required for testing, especially in the case of large volume retroviral supernatant production lots; 2) revises the time points tested and types of assays which should be used to monitor patients who are treated in gene therapy clinical trials which involve the use of retroviral vectors; and 3) changes the recommendation for life-long monitoring from active monitoring on an annual basis to collection and archiving of patient samples and tracking of relevant clinical history on an annual basis.

A retroviral vector supernatant standard has been developed to aid in measurement of assay sensitivity. Availability of this standard supports the use of a statistical approach for determination of volume of retroviral supernatant to be tested. In addition, the retroviral supernatant standard will provide a tool for comparing the sensitivity of RCR detection by different labs and/or testing methods and may lead to improvements in assay sensitivity.

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APPENDIX

1-1. Derivation of Recommendation for Test Volume for RCR Detection

Assuming the RCR are present in the production lot at a concentration (**c**) and that an assay will detect a single retrovirus in the sample, the probability (**p**) of detecting retrovirus in a volume (V_t) is given by the formula: $p= 1-\exp(-cV_t)$, because the number of RCR in V_t follows a Poisson distribution with a parameter cV_t. Solving for V_t, one gets the following equation:

$$V_t = -(1/c) \ln (1-p),$$

where **ln** denotes the natural logarithm.

Value for p

For the use of this formula, it is recommended that the value for **p** be set at 0.95. With the recommended replicate size and number defined in Appendix 1-3, **p** becomes the probability of detecting an RCR in the production lot.

Value for c

It is recommended that the value for **c** be set no higher than 0.01 RCR/ml or 1 RCR/100 ml. If the concentration of RCR in the production lot is 0.01 RCR/ml or greater, then the probability of detection is at least 0.95. If the production lot contains RCR at a concentration of <0.01 RCR/ml, the RCR may not be detected and would be administered to the patient.

Value for V_t

With the recommended value for **p** and **c**, the total volume of retroviral supernatant to be tested, independent of lot size, is calculated as follows:

$$Vt = -(1 / 0.01 \text{ RCR/ml}) \ln (1 - 0.95) \cong 300 \text{ ml}$$

Proposals to use smaller volumes should be developed and reviewed in consultation with CBER.

1-2. Empirical Determination of Assay Sensitivity

In collaboration with the ATCC, a standard retroviral stock (ATCC # VR-1450) has been established for use in determination of sensitivity and validation of assays used to detect the presence of replication competent retrovirus which would be produced from VPC containing amphotropic envelope. This stock can be used to determine the relative assay sensitivity for detecting RCR. This information can subsequently be used to determine the size of replicates of retroviral supernatant to be tested that will ensure

detection of a single retrovirus and thus, the number of replicates to ensure an adequate total volume, $\mathbf{V_t}$, as specified in this guidance (see Appendix 1-3). The virus stock is derived from a cell line which has been transfected with a molecular clone encoding Moloney murine leukemia virus (MoMLV) with a substitution of the envelope coding region from the 4070A strain of amphotropic murine leukemia virus (A-MLV) (Ref. 7). Therefore, this virus stock represents a typical recombinant virus that could be generated in a retroviral packaging cell line containing coding sequences for a MLV envelope. The infectious titer of the viral stock prepared by ATCC was determined using the direct S^+L^- PG-4 assay (Ref. 1). The stock was independently assessed for infectious titer by several different laboratories. The result of this analysis established the infectious titer +/- SD of the first lot of virus stock to be 6.9×10^7/ml (standard deviation for three experiments is 2.0×10^7/ml). Thawing and refreezing of the material appeared to result in a lower detectable infectious titer of 3.7×10^6/ml (standard deviation of 4.7×10^6/ml). Periodically, the vector stock will be replenished and the infectious titer of the new stock evaluated in comparison to the first lot.

The standard virus stock and its infectious titer can be used as a positive control to empirically determine the relative sensitivity of assay methods used for detection of RCR in retroviral vectors. In particular, this stock will allow investigators to determine the largest test volume in which a single RCR can be detected. The determination should be performed in the presence of a retroviral vector supernatant typical of a production lot in order to control for inhibitory effects of the retroviral vector particles on detection of RCR. Availability of this standard should allow individual investigators to establish this methodology in their own laboratories, as well as allow exploration of alternative methods for detection of RCR.

1-3. Formula to Determine Replicate Size and Number

Depending on the volume in which a single RCR can be detected by an individual RCR assay (as determined by use of the RCR standard, Appendix 1-2), it may be necessary to divide the total test volume into several replicate samples to ensure the detection of RCR in the sample. The number of replicates (**r**), can be determined using the formula,

$$\mathbf{r = V_t / V_s},$$

where $\mathbf{V_s}$ is the volume in which one RCR can be consistently detected (see Appendix 1-2 for determination of $\mathbf{V_s}$). For example, if 1 RCR can be detected in 2 ml, then the total test volume of 300 ml may be tested in 300/2 = 150 replicates of volume $\mathbf{V_s}$ or 150 2-ml replicates.

European Medicines Agency

London, 17 December 2009
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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON THE RISK-BASED APPROACH ACCORDING TO ANNEX I, PART IV OF DIR. 2001/83/EC APPLIED TO ADVANCED THERAPY MEDICINAL PRODUCTS

AGREED BY Cell Products Working Party, Gene Therapy Working Party and Biologics Working Party	November 2009
ADOPTION BY CAT/CHMP FOR RELEASE FOR CONSULTATION	17 December 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2010

Comments should be provided using this template to veronika.jekerle@ema.europa.eu

KEYWORDS	Risk-based approach, Risk identification, Risk factors, Advanced Therapy Medicinal Product, Gene Therapy Medicinal Product, somatic Cell Therapy Medicinal Product, Tissue Engineered Product, Marketing Authorisation Application Dossier Requirements

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

The aim of the risk-based approach as defined in Annex I, part IV of Dir. 2001/83/EC is to determine the extent of data required for Marketing Authorisation Application (MAA) for an advanced therapy medicinal product (ATMP). The risk-based approach is based on the identification of risk factors inherent to the nature of the ATMP in question and associated with its quality, safety and efficacy. The risk-based approach as defined in Annex I, part IV of Dir. 2001/83/EC should be distinguished from Risk Management, and the benefit / risk assessment in the context of a marketing authorization evaluation. The risk-based approach, when applied to the development program should be described and justified in Module 2 of the Marketing Authorisation Application dossier.

The risks associated with an ATMP are highly dependent on the biological characteristics and origin of the cells, the manufacturing process, and the biological characteristics of used vectors, the properties of protein expression, non-cellular components and the specific therapeutic use of the ATMP. Thus the manufacturing process including in-process testing and batch release testing should be adequate to limit the risk of the ATMP. Nonclinical and clinical testing should further address the identified risk factors.

2. PROBLEM STATEMENT

The guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) and the Note for Guidance on gene transfer medicinal products (CPMP/BWP/3088/99) addressed the manufacturing and quality control as well as non-clinical and clinical development of respectively cell-based medicinal products (which includes somatic cell therapy medicinal products and tissue engineered products) and gene therapy medicinal products. Revision of Annex I part IV of Directive 2001/83/EC, which followed the entry into force of Regulation (EC) No. 1394/2007 for ATMPs, introduced the concept of the risk-based approach. However, no detailed guidance on the practical application of the risk-based approach and the consequences for the product development are available so far. Moreover, there is a necessity to familiarise the stakeholders, future applicants, National Competent Authorities as well as consumer with this concept.

This concept paper is intended to provide the background and rationale of the guideline on the risk-based approach and shall describe the approach and content of the future guideline.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The use of ATMPs may be associated with certain risks, which are linked to several risk factor related to the Quality, biological activity and administration of the ATMP. Individual risk factors shall be discussed in order to enable a conclusion on the overall risk of the ATMP.

A non-exhaustive list of risk factors for cell-based and gene therapy medicinal products is given below:

Cell based medicinal products:

Risk factors, e.g.

- The cells used including cell source, cell type and differentiation status
- All aspects of the manufacturing process including manipulation
- The non-cellular components
- The specific therapeutic use including mode of administration, duration of exposure

The risk factors may be linked with risks such as

- Unwanted immune responses as target or effector cell
- Genetic instability and tumorigenicity of the cells used
- The transmission of viruses and adventitious agents
- Undesired immunogenic, pyrogenic or toxicological reactions by non-cellular components
- Unintended biological responses of the product

Gene therapy medicinal products:

Risk factors, e.g.

- Potential for and extent of chromosomal integration of a vector
- Capacity of a vector/ gene for latency/ reactivation
- Capacity of a vector for inadvertent replication after complementation by viruses causing escape from latency and reactivation and eventually leading to mobilisation
- Replication incompetence or competence of a vector
- Potential for recombination or re-assortment
- Altered expression of (a) host gene(s)
- Transgene expressed and its duration
- Biodistribution
- Potential for shedding and transmission

The risk factors may be linked with risks such as

- Unwanted immune responses
- Tumorigenicity
- Infection
- Unintended biological responses of the product

4. RECOMMENDATION

The CPWP and GTWP recommend drafting a guideline on the application of the risk-based approach for ATMPs. It is proposed that the guideline has two separate sections on aspects specific to cell-based medicinal products and gene therapy medicinal products, respectively. Furthermore aspects regarding combined ATMPs will be addressed.

The guideline is intended to provide an approach on how to identify and describe the risks of an ATMP in the MAA dossier. It is not the intention to provide a rigid classification system of different risks but rather to exemplify the concept by using several examples with different risk profiles (i.e. a genetically modified stem cell product of allogeneic and/or xenogeneic nature or an autologous cell-based product of locally administered differentiated cells).

It is foreseen that the application of the risk-based approach shall follow the following basic steps:

1) **Risk Identification of the ATMP:**

   The Applicant is asked to propose a systematic process for the identification and discussion of risks to the quality, safety and efficacy of an ATMP. The risk shall be based on individual risk factors, such as the ones listed above. The Applicant's conclusion on the degree of risk should be thoroughly justified on the basis of scientific data underpinning identified risk factors.

2) **Consequences for the extent of data in the MAA dossier:**

Based on the identification and discussion of the risk of an ATMP, the Applicant should justify the extent of quality, non-clinical and clinical data presented for Marketing Authorisation Application and provide an overview of the implement in the MAA dossier. The extent of data shall take into account the technical requirements for ATMPs as described in Annex I, part IV of Dir. 2001/83/EC. Depending on the risk of the product certain chapters may be emphasised and complemented with additional data, where necessary, or limited when appropriately justified on the basis of the risk.

In order to address these risks, certain minimisation activities need to be conducted and measures implemented during the product lifecycle.

The approach described in this guideline should enable the applicant to establish an adequate development strategy for an ATMP, including but not limited to adequate in-process controls, setting of specifications, non-clinical data and clinical data requirement. These issues will also be illustrated by examples of products with different risk profiles.

Within the MAA dossier, the risk-based approach shall be placed into Module 2 of the Common Technical Document as a supplement to the quality, nonclinical and clinical overall summaries. Further guidance to applicants on the practical aspects of the chapter on the risk-based approach will be provided in the guideline.

5. PROPOSED TIMETABLE

It is anticipated that a draft guideline will be available within 12-18 months after adoption of the concept paper and will be released for 6 months external consultation, before finalization within a further 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The development of a guideline on the risk based approach will be led by CPWP and GTWP (1 common coordinating drafting group) in collaboration with BWP (consulted for quality aspects), with SWP (consulted for non-clinical aspects), with PhVWP (consulted on the complementarity of this approach with the risk analysis and risk management activities in place), and in compliance with directions given by the CAT. Other relevant working parties and relevant scientific committees e.g. PDCO and CHMP and external parties will be consulted as needed.

Drafting work will be conducted primarily by email and teleconferences. The relevant working parties will discuss draft versions at or in the margin of their regular meetings.
Based on the multidisciplinary nature of this revision, it is considered that a minimum of two dedicated face-to-face drafting group meeting will be necessary.

7. IMPACT ASSESSMENT (ANTICIPATED)

The guideline on the application of the risk-based approach is expected to clarify the process (analysis, methodology, and presentation) of the determination of the extent of data requirements needed for marketing authorisation application of an ATMP. The guideline is also intended to help regulators in the assessment of the MAA dossier. It may contribute to streamline the development, enabling the applicant to establish an adequate development strategy and ultimately marketing authorisation of applications of ATMP via the centralised procedure.

8. INTERESTED PARTIES

Pharmaceutical industry and academic or other developers of ATMPs, academic networks and learned societies involved in the area.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

- Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on Advanced Therapy Medicinal Products
- Commission Directive Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products.
- Guideline on Human Cell-based Medicinal Products (EMEA/CHMP/410869/2006)
- Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99)
- Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products (EMEA/149995/2008)

European Medicines Agency

London, 20 November 2008
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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON SAFETY AND EFFICACY FOLLOW-UP - RISK MANAGEMENT OF ADVANCED THERAPY MEDICINAL PRODUCTS

DRAFTING GROUP DISCUSSION	December 2007 to February 2008
DISCUSSION IN GTWP, CPWP, PHVWP	February and March 2008
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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

EXECUTIVE SUMMARY

Scientific progress in cellular and molecular biotechnology has led to the development of advanced therapy medicinal products, such as gene therapy, somatic cell therapy, and tissue engineering products. The European parliament and the Council have issued Regulation No 1394/2007 (hereafter referred as the Regulation) that set up specific rules for advanced therapy medicinal products (ATMPs).

Article 14 (4) of the Regulation requests the European Medicines Agency to draw up detailed guidelines relating to the post authorisation follow-up of efficacy and adverse reactions, and risk management. To meet this requirement, this guideline has been prepared by the EMEA and its scientific committees and working parties. It should be read and understood in conjunction with existing relevant guidelines, and provides a basis for the development of future detailed guidelines in the field.

The scientific rationale for specific rules for pharmacovigilance of advanced therapies is described as a list of main points that should be considered when preparing a risk management plan for advanced therapy medicinal products (ATMP.)

Safety and efficacy follow-up systems form part of the Risk management system and should be planned in the EU-Risk management plan (EU-RMP). Both follow up systems are defined as any systematic collection and collation of data that is designed in a way that enables learning about safety and/or efficacy of an ATMP. It may include passive or active surveillance, observational studies, or clinical trials. It is stressed that both the efficacy and the safety follow-up systems are not a substitute for the need for adequate data to be available at the time of authorisation to enable proper benefit-risk evaluation.

Two documents that are part of a marketing authorisation application are directly affected by this guideline – the EU Risk Management Plan (EU-RMP) and the Detailed Description of the Pharmacovigilance System (DDPS). It may be necessary to introduce additional elements to the description of the pharmacovigilance system to take account of the particular issues with ATMPs. In Part I of the EU-RMP, a new chapter for ATMPs is introduced within the section Additional EU Requirements of the Safety Specifications. Groups of risks that are more targeted to ATMPs should be discussed there in an order that follows the procurement in living donors, the product manufacturing, administration, and follow-up of patients. Part II of the RMP shall contain a new discussion on the need of efficacy follow-up. If the need is identified, details of an efficacy follow-up plan should be submitted as Annex 9 of the RMP.

The guideline also lists some points to be considered for efficacy post-authorisation studies, in particular sample size, use of data, reporting, choice of endpoints and examples of events of particular interest.

It is also acknowledged that support of electronic exchange of pharmacovigilance information will need some adjustments. It will be addressed with EudraVigilance stakeholders separately

Consequences of non-compliance with the agreed risk management plan include financial penalties and regulatory measures. These are outlined in the guideline as requested by stakeholders in the public consultation.

Follow-up systems, risk management and traceability need processing of personal data. Related data protection issues are therefore briefly discussed with focus on legal situation and feasibility.

GUIDELINE ON SAFETY AND EFFICACY FOLLOW-UP - RISK MANAGEMENT OF ADVANCED THERAPY MEDICINAL PRODUCTS

TABLE OF CONTENT

1. INTRODUCTION

Scientific progress in cellular and molecular biotechnology has led to the development of advanced therapies, such as gene therapy, somatic cell therapy, and tissue engineering. Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tailored and harmonised rules are needed to guarantee a high level of health protection, as well as to harmonise and facilitate market access, foster competitiveness and provide legal certainty.

The European parliament and the Council have issued Regulation No 1394/2007 (hereafter referred as the Regulation) that sets up specific rules for advanced therapy medicinal products (ATMPs). It regulates those ATMPs which are intended to be placed on the market in the European Economic Area, and that are within the scope of Directive 2001/83/EC as amended, i.e. products that are either prepared industrially or manufactured by a method involving an industrial process.

In its Chapter 5 the Regulation details post-authorisation requirements. Article 14 (4) specifically requests the European Medicines Agency to draw up detailed guidelines relating to the post authorisation follow-up of efficacy and adverse reactions, and risk management. In order to meet this request, the EMEA is issuing this guideline to complement the existing relevant guidelines. It should also provide a basis for the development of future detailed guidelines in the field.

This guideline concerns an area where knowledge is fast evolving and there is limited experience. Marketing authorisation applicants and holders are encouraged to apply for scientific advice from the EMEA as early as possible to prevent unnecessary mistakes in development and delays in the regulatory process.

The guideline provisions are of "overarching" character, which means that they describe a framework of regulatory requirements applicable to all ATMPs. Specific provisions for gene therapy, cell therapy and tissue engineering products continue to be included in product type specific guidelines.

In the foreseeable future, it is expected that with growing experience and establishment of the Committee on Advanced Therapies (CAT), there will often be a need to update the guidelines concerning ATMPs. Therefore, users of this guideline should always check whether a newer guideline has been published which further specifies the issues discussed below.

It needs to be highlighted that the concept for generation of long-term data in post-authorisation phase is not a substitute for the need for efficacy and safety data at the time of marketing authorisation application. Quality, safety and efficacy data are required as the basis for approval and should be sufficient to enable a proper benefit-risk evaluation. Any lack of such data and the intention to generate post-authorisation data should be fully justified at the time of marketing authorisation application. Due to the novelty of these products, applicants are encouraged to seek scientific advice from the EMEA also in respect of risk management plans.

To ensure optimal assessment processes, regulatory authorities are encouraged to use multidisciplinary teams for assessment of risk management plans, particularly when the plan contains efficacy follow-up activities.

2. SCOPE OF THE GUIDELINE

The Regulation defines ATMPs as gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products. This guideline focuses on unique characteristics of ATMPs as further detailed in the Chapter 6 - Scientific Rationale. Its applicability is restricted to ATMPs.

This guideline describes specific aspects of pharmacovigilance, risk management planning, safety and efficacy follow-up of authorised ATMPs, as well as some aspects of clinical follow-up of patients treated with such products. The target audience includes in particular marketing authorisation holders, competent authorities for medicinal products, and health care providers, irrespective whether of commercial or non-commercial character.