

Current European Guidance on Monitoring for Insertional Mutagenesis

Matthias Schweizer

Paul-Ehrlich-Institut
Federal Institute for Vaccines and
Biomedicines

Bethesda, Dec 10, 2010



Use of ATMPs in Europe

Authorized Medicinal Product:

MA exclusively by centralized procedure via CAT / CHMP

up to now:

no MAA für retro- or lentiviral vectors or cells modified by them

Clinical Trials:

In the responsibility of the member states!

Compassionate use:

(for chronically or seriously debilitating diseases or life-threatening diseases, cannot be treated satisfactorily by an authorised medicinal product, medicinal product subject of an application for a MAA or under investigation in clinical trials)

regulated by member states!

Hospital exemption:

(for ATMPs prepared on a **non-routine basis**, used in a **hospital under the exclusive professional responsibility of a medical practitioner**, custom-made product for an **individual patient**)

authorized by member states!



Harmonization of Clinical Trials in Europe

Implementation of the **Clinical Trials Directive** 2001/20/EC (in 2004)

EUDRA-CT: Data bank on clinical trials in EU (since 2004)

trials initiated before 2004 are not cited in EudraCT

At present: 8 clinical trials using gamma-retroviral vectors
8 clinical trials using lentiviral vectors

for multinational clinical trials:

Initiation of a **Voluntary Harmonisation Procedure** (VHP)

(Pilot phase ongoing)

(coordinated by **Clinical Trials Facilitation Group**, CTFG)

Development of **scientific guidelines**

(including specific gene therapy guidelines)



EU Guidelines Relevant for Insertional Mutagenesis

Note for guidance on the quality, pre-clinical and clinical aspects of **gene transfer medicinal products** (*in revision*)

Quality, pre-clinical and clinical aspects of medicinal products containing **genetically modified cells** (*Draft*)

Non-clinical studies required **before first clinical use** of gene therapy medicinal products

Follow-up of patients administered with gene therapy medicinal products

Guideline on development and manufacture of **lentiviral vectors**

Guideline on the **risk-based approach** according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products (*Draft*)

European Pharmacopoeia:

5.14. Gene Transfer Medicinal Products for Human Use:

- Genetically modified cells
- Retroviridae-Derived Vectors for Human Use



Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

Draft¹ (end of consultation)

20 May 2010

EMA/CHMP/GTWP/671639/2008

Committee for the Medicinal Products for Human Use (CHMP)

Quality Aspects

Characterization

- The **gene copy number** per cell should be justified
- the **integration profile** should be studied in **relation to known oncogenes/tumour suppressor genes**, where applicable.
- clonality and chromosomal integrity** of the cell population derived from the genetically modified cells should also be studied



Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

Draft¹ (end of consultation)

20 May 2010

EMA/CHMP/GTWP/671639/2008

Committee for the Medicinal Products for Human Use (CHMP)

Non-Clinical Aspects

Toxicology

-the **number of integration sites** and their characterisation, if feasible, as far as **adjacent gene identity and function**, should be discussed in relation to clinical application.

-Special attention should be paid to **activation of oncogenes** and/or inactivation of tumour suppressing genes and **risk of insertional mutagenesis**.

-If genetically modified primary cells are shown to have a clonal integration profile, and /or integration is found within oncogenes or tumour suppressor genes, **oncogenesis studies** are required.



Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

Draft¹ (end of consultation)

20 May 2010

EMA/CHMP/GTWP/671639/2008

Committee for the Medicinal Products for Human Use (CHMP)

Clinical Aspects

Pharmacokinetics

Attention should be paid to ... **proliferation ... of the genetically modified cells**. The methodology used and its limitations should be discussed.

Clinical safety

...**special risk for delayed effects associated with the integrated vector** and its expressed products **should be considered** (e.g. **oncogenesis**, ...).

The **safety database should be large enough** to detect common short- and long-term adverse events that may be associated with the use and/or application procedure of the genetically modified cells.



Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells

Draft¹ (end of consultation)

20 May 2010

EMA/CHMP/GTWP/671639/2008

Committee for the Medicinal Products for Human Use (CHMP)

Pharmacovigilance

Genetically modified cells **may need specific long-term studies** to monitor safety issues... .

The long-term safety issues, such as **malignant transformation** ... should be addressed in the **Risk Management Plan**.



GUIDELINE ON THE NON-CLINICAL STUDIES REQUIRED BEFORE FIRST CLINICAL USE OF GENE THERAPY MEDICINAL PRODUCTS

London 30 May 2008

EMA/CHMP/GTWP/125459/2006

4.2 Minimal requirements for non-clinical studies on GTMP before first use in human subjects

Genetically-modified somatic cells

In vitro and/or, when applicable, in vivo studies should be used to examine effects on

cellular morphology, phenotype, function and behaviour,
such as proliferation, differentiation, immortalisation or the induction of a transformed phenotype.

... The **integration sites** should be characterised for adjacent gene identity and function, where feasible

Special attention should be paid to **activation of oncogenes** and/or **inactivation of tumour-suppressing genes**.

The impact of **copy number** in single cells should also be evaluated



GUIDELINE ON FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS

London, 22 October 2009

Doc. Ref. EMEA/CHMP/GTWP/60436/2007

4.3.1 Viral vectors which can integrate or have the potential for latency followed by reactivation

It is recommended that patients enrolled in clinical GT medicinal product trials, where non-clinical tests or evidence from other clinical trials using identical vectors or modifications of vectors indicate a **potential for integration** or late re-activation have a **monitoring plan** with a brief clinical history and sample testing at the following time points: **pre-treatment, 3, 6 and 12 months after treatment for at least 5 years, and then yearly** until data indicate that **there is no longer any risk** to be followed.

If any post-treatment samples are positive, indicating integration or re-activation, or ***clinical evaluation indicate a treatment induced side-effect/adverse event***, then **a more regular and extensive clinical follow-up** should be undertaken.

Similar in: GUIDELINE ON SAFETY AND EFFICACY FOLLOW-UP – RISK MANAGEMENT OF ADVANCED THERAPY MEDICINAL PRODUCTS, Doc. Ref. EMEA/149995/2008



Risk-based approach and insertional mutagenesis

Risk-based approach (Directive 2009/120/EC)

- may be applied to determine the extent of Q/N-C and C data
- risk factors include
 - nature of gene therapy product
 - extent of replication-competence of viruses
 - **level of integration into the genome**
 - **risk of oncogenicity**
 - mode of administration....
- non-clinical/clinical experience with other (related) ATMPs
- kind of the disease. Patients treated

Guideline in progress



Conclusion:

Necessity to assess risk of insertional mutagenesis / genotoxicity is addressed in a number of guidelines.

(Quality, non-clinic, clinical monitoring, follow up)

Detailed guidelines on criteria for authorization, monitoring, or stopping rules are not available due to the limited experience and complexity of these kind of products.



In practice:

Monitoring and stopping rules have to be justified in the clinical trial application by the applicant.

The constitution of a safety monitoring board is recommended.

Prior application, applicant may ask for Scientific Advice of respective national authority.

With a view to MA, Scientific Advice can be requested at EMA.

Decisions of competent authorities are

based on knowledge on state-of-the-art of science and technology

and have to be made ***case by case,***

in accordance with available guidelines and recommendations of expert groups, e.g. of the GTWP of CAT, GTAC, RAC, Clinigene, external scientific and clinical experts.



In case of SUSAR: (recently in Germany)

Principal investigators of clinical trials dealing with the same or similar IMP have to provide an updated benefit/risk assessment, maybe based on additional monitoring of the patients enrolled. Decision on continuation of the trial is made case by case.



Point to be considered in case-by-case decisions

Vector design

Gamma? Lenti? SIN? Promoter, Enhancer, WPRE, Insulators etc.? Envelope?

Type of cells

stem cells? Degree of differentiation?

Culture condtions

growth factors, transfection methods, copy number ?

Patient characteristics

age, disease, conditioning?



Frequently asked questions to regulators

Suitability of literature data on „similar“ products in place of product characterization, non-clinical or clinical data collected with the IMP?

Extent of non-clinical or clinical studies required after change of product, e.g. from conventional to SIN vector, change of promoter, etc.



Summary:

Many general guidelines available,

Decisions on case by case basis,

Discussion of regulators and non-regulatory experts essential



Acknowledgements

Klaus Cichutek
Christian Buchholz
Brigitte Anliker
Matthias Renner

Thank you for attention!

<http://www.pei.de/>

