Federal Institute for Vaccines and Biomedicines

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Gene therapy products for Clinical Trials – Advice on data requirements

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Gene therapy products for Clinical Trials – Advice on data requirements

AGENDA

- Definition
- Basic information
- Quality considerations
- Non-clinical considerations
- Conclusion

How is Gene Therapy defined ??

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

Member States shall put into force by the 5 April 2010 at the latest.

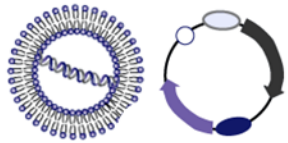
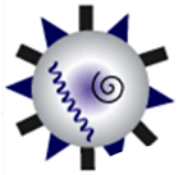
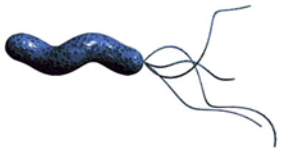
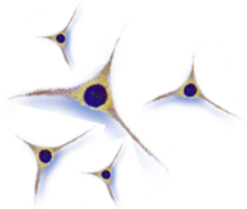
Gene therapy medicinal product

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

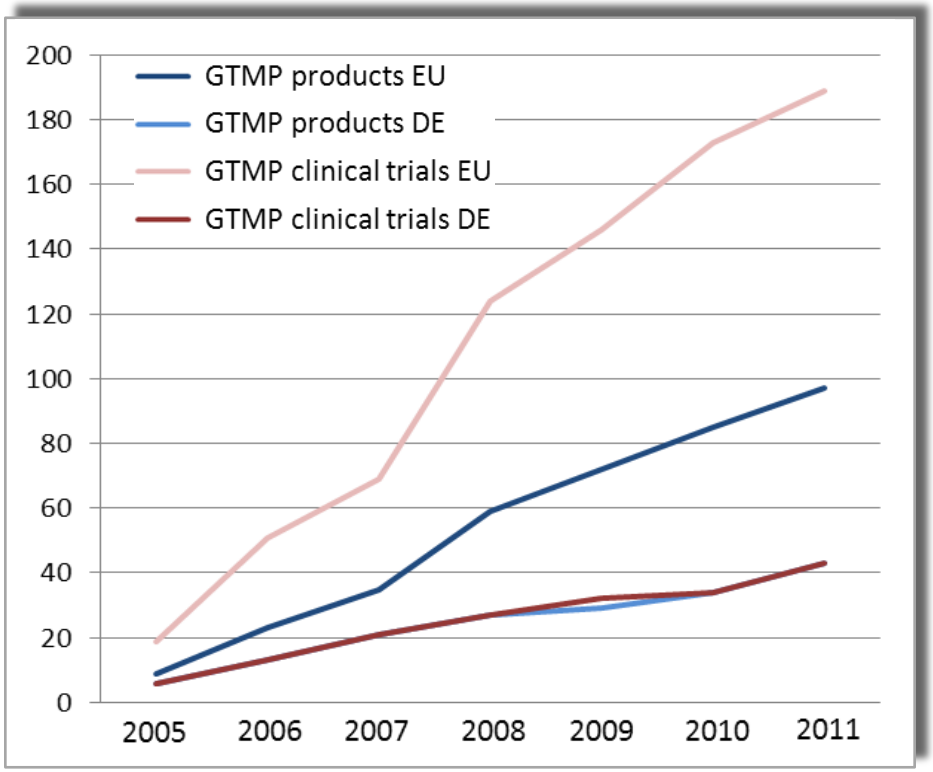
(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

Type of drug substances in GTMPs		Examples
(a) recombinant nucleic acid sequence(s)		- oligonucleotides (of biological origin) - plasmid DNA → naked or formulated with synthetic delivery systems such as lipids, polymers and/or peptide ligands
(b) genetically modified virus(es)		- replication-deficient - replication-competent - conditionally replication-competent → e.g. retrovirus, adenovirus, adeno-associated virus, herpes simplex, vaccinia virus
(c) genetically modified microorganism(s)		- *Mycobacterium bovis* (BCG), *Shigella, Clostridia* → genetically modified e.g. by plasmids
(d) genetically modified cells		- autologous, allogeneic, xenogeneic - primary cells or stable cell lines → genetically modified by one of the products described above

GTMP Clinical Trial Applications in EU & Germany

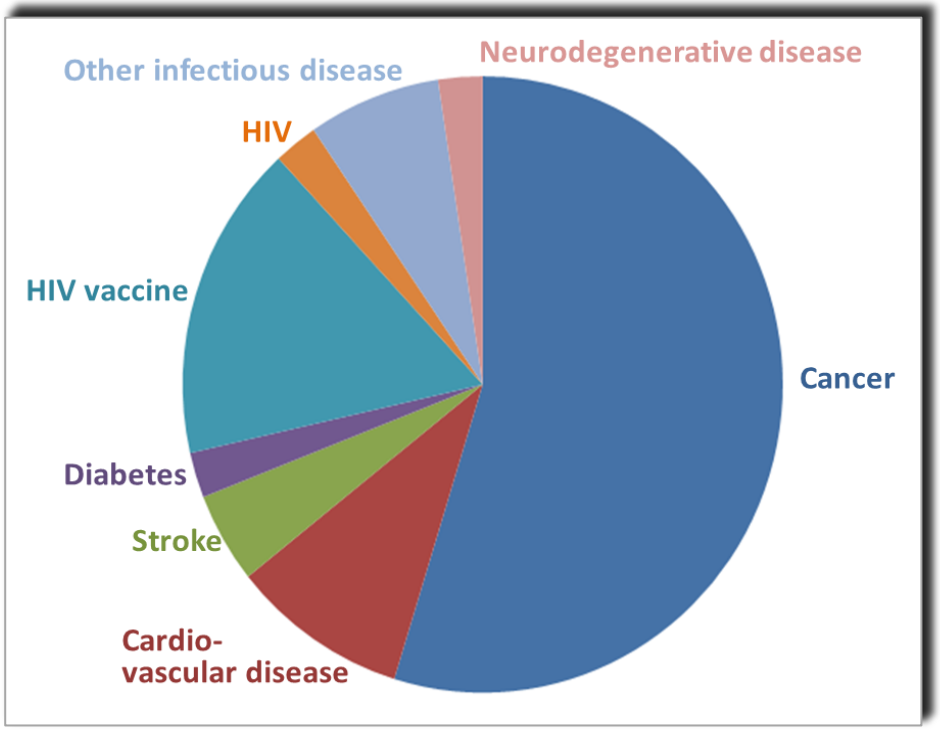


GT clinical trials in Germany by year and clinical phase

GTMPs	Phase I	Phase II	Phase III
2005	1	3	2
2006	5	1	1
2007	3	2	3
2008	1	4	1
2009	1	1	1
2010	1	2	1
2011	4	2	3
in total: 43	16	15	12

2005 to 3Q 2011

GTMP Clinical Trial Applications in Germany (PEI)



Clinical trials according to §40 AMG (2005-2011)

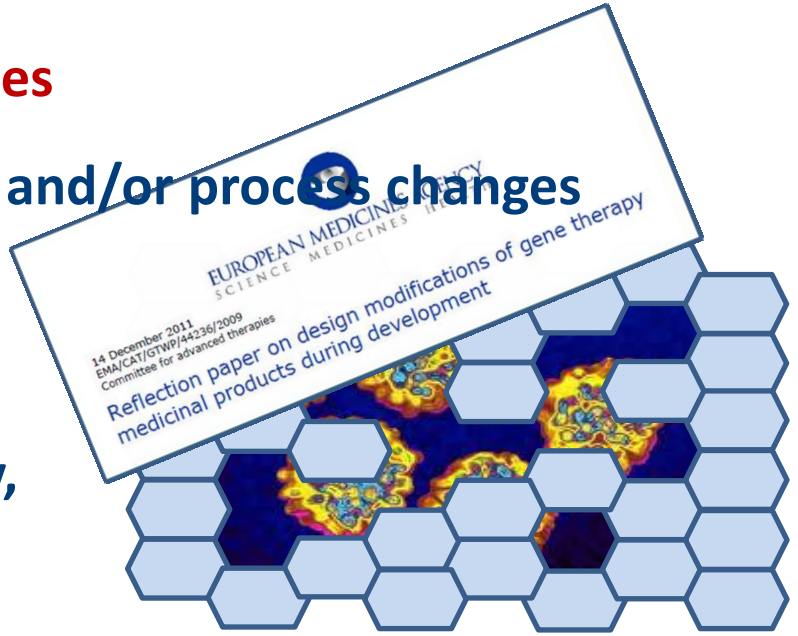
Adenovirus	5	(5)
γ-retroviral vectors	4	(0)
Plasmid-DNA	10	(7)
MVA	11	(11)
AAV	3	(1)
HSV (cond.-repl.)	2	(2)
Parvo (cond.-repl.)	1	(1)
Reo (cond.-repl.)	1	(1)
Vaccinia (cond.-repl.)	2	(2)
Salmonella	1	(0)

() = in vivo application

August 2005 – October 2011
sorted by indication and vector type

Measures to ensure good GTMP quality

- ✘ Quality and control of **starting material** (MCB, WCB, bacterial cell bank, plasmids, MVS, (producer) cells)
- ✘ Understanding of the **manufacturing process** and the **characteristics** of the product
- ✘ Meaningful **in-process controls**, test of intermediate products, measure process variables, realtime – rapid - quantitative assays
- ✘ Determine type and levels of **impurities**
- ✘ Ensuring **comparability** upon product and/or process changes
- ✘ Establish potency assay for **biological activity**
- ✘ Release specifications ensuring safety, **identity, purity and potency** of the final product



Characterisation/release of GTMPs

Identity/ genomic integrity	- of transgene and vector (immunochemically, NAT, sequence)
Bioactivity/Potency	- infectivity (infectious particles), transduced cells, gene copy number - particles to infectious titer ratio - transgene expression - bioactivity/function
Purity	- RCV (replication competent virus) - host cell + `production system´ protein - host cell + `production system´ DNA - residual reagents (antibiotics, benzonase, BSA) - sterility (bacterial, fungal) - adventitious agents, mycoplasma, bacterial endotoxin
Physico-chemical characteristics	- appearance, osmolality, pH - particle size distribution - vector aggregates

Scientific guidance for GTMPs I

Quality

CPMP/BWP/3088/99 Quali…

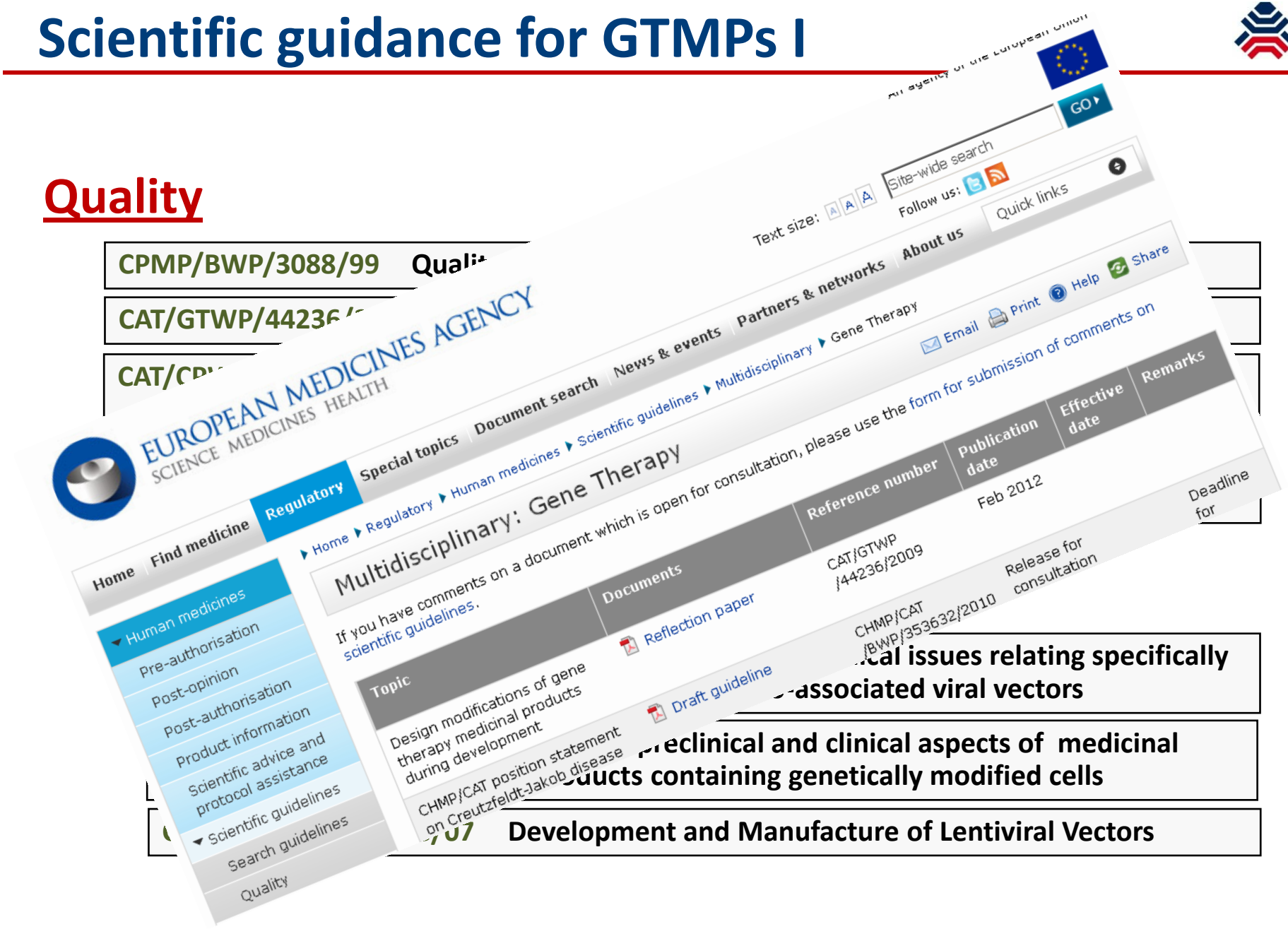
CAT/GTWP/44236/…

CAT/CPI…

…cal issues relating specifically …associated viral vectors

…preclinical and clinical aspects of medicinal …ducts containing genetically modified cells

…/07 Development and Manufacture of Lentiviral Vectors



Scientific guidance for GTMPs II

Quality

➢ Ph. Eur. 5.2.3. Cell substrates for the production of vaccines for human use

Table 5.2.3.-1 – *Testing of cell lines*

Test	Cell seed	Master cell bank (MCB)	Working cell bank (WCB)	Cells at or beyond the maximum population doubling level used for production
1. IDENTITY AND PURITY				
Morphology	+	+	+	+
Identification: nucleic acid fingerprinting and a relevant selection of the following tests: biochemical (e.g. isoenzymes), immunological (e.g. histocompatibility), cytogenetic markers	+	+	+	+
Karyotype (diploid cell lines)	+	+	+(1)	+(1)
Life span (diploid cell lines)				
Bacterial and fungal contamination				
Mycoplasmas				
Spiroplasmas (insect cell lines)				
Electron microscopy (insect cell lines)				
Tests for extraneous agents in cell cultures				

EUROPEAN PHARMACOPOEIA 6.0

5.14. Gene transfer medicinal products for human use

01/2008:51400
corrected 6.0

5.14. GENE TRANSFER MEDICINAL PRODUCTS FOR HUMAN USE

3. Notification

on the clinical trial of medicinal products for human use.

A joint publication of the Federal Institute for Drugs and Medical Devices and the Paul Ehrlich Institute

for the request to the competent authority for the authorisation of a clinical trial according to § 40 para. 1 sentence 2 of the German Medicines Act (*Arzneimittelgesetz*, AMG), as well as § 7 of the statutory regulation according to § 42 para. 3 of the AMG (GCP-V) for the notification of subsequent amendments during the conduct of the clinical trials according to § 10, as well as for the notification of the end of the clinical trial according to § 13 paragraph 8 and 9 of this statutory regulation.

August 10, 2006

ICH harmonisation for better health

Considerations:

CHMP/ICH/607698/08 Oncolytic Viruses

London, 20 April 2009
Doc. Ref. EMEA/CHMP/VWP/141697/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON QUALITY, NON-CLINICAL AND CLINICAL ASPECTS OF LIVE RECOMBINANT VIRAL VECTORED VACCINES

Aim of non-clinical studies

- pharmacodynamic "proof of concept" in non-clinical model(s)
- biodistribution of the GTMP
  - identification of potential target organs of toxicity
  - identification of potential target organs of biological activity
- recommendation on initial dose and dose escalation scheme to be used in the proposed clinical trial
- identification of toxic effects including immunogenicity and tumorigenicity
- identification of parameters to be monitored in the proposed clinical trial
- identification of patient eligibility criteria

Non-clinical overview

- GTMP biological characteristics depend on vector, transgene + its product
- biological / toxicological /pharmacological activity needs to be shown for transgene + vector on cells
- test material ideally should be identical to clinical lot
- GLP compliance of tox and biodistribution studies?
- choice of animal model to explore transgene effects and therapeutic function

Considering animal model selection

- selection of relevant species and model systems (immune compromised, knockout and transgenic)
  - susceptible to infection with the vector, resembles human receptor distribution pattern
  - comparable activity of regulatory vector sequences
  - models immune response
  - reflect biological response to the transgene product
  - immune status of the animal model
- homologous models (e.g. to test immungenicity, immune modulators as transgene) or disease models (e.g. for oncolytic vectors) may be appropriate.

Biodistribution

- for target and non-target organs
- analysis of distribution, persistence, clearance, mobilisation, transcription of transgene (product)/vector
- observation time ideally until there is no signal detection
- route of administration, treatment regime, dosing should mimic clinical situation, and potentially worst case scenario
- specificity, duration of gene expression and activity in target tissues, if target tissue selectivity is expected
- potential need for integration studies
- biodistribution studies should also address the risk of germ line transmission

Aspects of toxicology

- virulence, integration and replication capacity, latency/reactivation, etc. of the GTMP
- recombination might lead to virulence, to RCVs, to integration
- inadvertent replication after complementation by wt-virus might occur
- interaction with concomitant medication
- toxicological consequences of any aberrant gene product (might have different immunogenicity profile), non-therapeutic vector proteins, and other impurity profile
- re-administration to patients might cause host immune response to GTMP
- in vivo studies might be hampered by vector-host specificity

The risk-based approach

Risk profiling:
A method to systematically integrate all available information on risks and risk factors to obtain a profile of each individual risk associated with a specific ATMP

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***

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

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

The risk-based approach – example

Step 3: Matrix table to map risk factor/risk relationship

AAV-vector expressing a fictitious enzyme to treat a metabolic deficiency

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Toxicity resulting fro unintended alteratio therapeutic gene exp
Recombination/mobilisation	Recombination may lead to replicating AAV. Tumor formation depends on level of AAV genome integration into host genome. Addressed in CTD 3.2.P.5 - Control of DP and CTD 4.2.3 –Toxicology (toxicology/integration studies).	Recombination / Mobilisation may lead to increased immunogenicity due to higher number of vector / RCV particles. Addressed in CTD 3.2.P.5 - Control of DP and CTD 4.2.3 -Toxicology.	Recombination during manufacture might lead to loss of the transgene and consequently loss of function. Addressed in CTD 3.2.P.5 - Control of DP.	Mobilisation (with wt ar coinfection) might resu higher levels of therap gene expression. Toxi other than immunogen to overexpression is co to be low. Addressed ir 4.2.1 - Pharmacology a 4.2.3 - Toxicology stud justified by literature information.
Integration	AAV vectors are able to integrate into the genome albeit at low levels. Integration studies are performed (CTD 4.2.3- Toxicology). See also risk factor 'biodistribution' (CTD 4.2.2 -Pharmacokinetics)			
Type of transgene and transgene expression levels		The therapeutic gene is of human origin and respective endogenous gene product in patients is present but defective. This might cause unwanted immunogenicity. Expression of therapeutic protein addressed and justified in CTD 5.3.5 -Reports of efficacy and safety studies.	Impaired transgene expression might lead to treatment failure. Transgene expression and potency studies and in vivo proof-of-concept studies. Addressed in CTD 3.2.P.5 - Control of DP and 4.2.1. - Pharmacology.	Over-expression of tra in target cells is not co to be of concern. Toxic other than immunogen to over-expression is considered to be low. 4.2.1 - Pharmacology, 4.2.3 - Toxicity and jus literature data.
Vector type	AAV is not known to be tumorigenic *per se*. A low potential of AAV for insertional mutagenesis exists (see RF 'integration'). Addressed in	AAV is known to be immunogenic. Addressed in immunogenicity and Toxicity studies (CTD 4.2.3), and Clinical safety studies (CTD 5.3.5 -	Pre-existing immunity to the vector might impair efficiency of treatment. Furthermore repeated administration may increase	
Biodistribution	Biodistribution of the vector contributes to the risk of tumour formation via vector persistence and integration events (see risk factor on integration). Inclusion of transduced non-target organs in studies on episomal/ integrated vector status. Addressed in CTD 4.2.2-Pharmacokinetics (biodistribution), CTD 4.2.3 – Toxicology (integration studies).	Biodistribution of the vector to non-target, immunogenic sites. Addressed in biodistribution / immunogenicity studies -CTD 4.2.2 - Pharmacokinetics (biodistribution), CTD 4.2.3 - Toxicology (immunogenicity), CTD 5.3.5 -Reports of efficacy and safety studies, (clinical safety).	Treatment failure might be induced by unwanted immunogenicity due to biodistribution to non-target, immunogenic sites. Addressed in biodistribution and long-term transgene expression studies. CTD 4.2.1 - Pharmacology and CTD 4.2.2 – Pharmacokinetics.	Toxicity as a result of transgene-overexpress non-target cells consid be low. Evaluation of t and transgene expressi levels in non-target tis cells. CTD 4.2.2 - Pharmacokinetics (biodistribution) and 4. Toxicology (toxicity)
Relevance of animal model		Animal model is not predictive for immunogenicity in patients due to differences in immune responses. An additional animal model to	Animal model may not be predictive for treatment failure due to differences in the immune status of animal and patients.	

Toxicology

- Same route/method/schedule of administration as in clinical protocol
- Dosing should mimic clinical situation, with appropriate safety margins
- Use of the most relevant animal model for the expected toxicological effects
- Observation time depends on type of product:
  - should reflect the duration of gene expression (refer to biodistribution)
  - multiple administrations might mimic effects of persist gene expression
- Repeated tox requirements dependent on clinical treatment regime
- Standard genotoxicity studies not required
- Evaluation of tumorigenicity in vitro, positive signals → in vivo testing
- Immunogenicity/immunotoxicity studies when factors (growth factors, cytokines) with an effect on the immune system are present/produced

Scientific guidance for GTMPs III

NC and Clinic

CPMP/BWP/3088/99 Quality, preclini

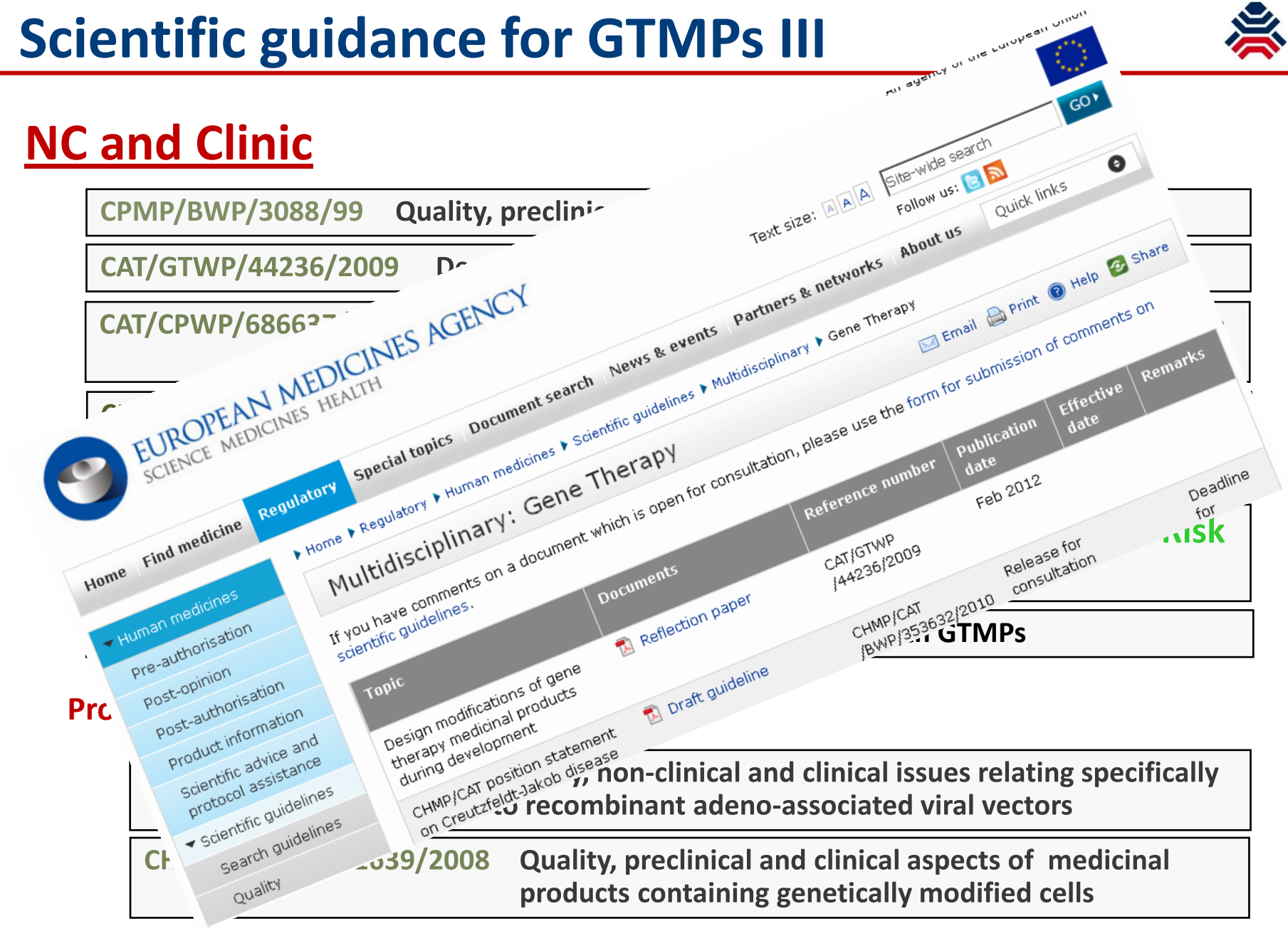
CAT/GTWP/44236/2009 D

CAT/CPWP/6866

Pro

, non-clinical and clinical issues relating specifically
o recombinant adeno-associated viral vectors

CH 639/2008 Quality, preclinical and clinical aspects of medicinal products containing genetically modified cells



Scientific guidance for GTMPs IV

NC + Clinic

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August 10, 2006

ICH harmonisation for better health

Considerations:

CHMP/ICH/607698/08	Oncolytic Viruses
CHMP/ICH/449035/09	General Principles to Address Virus and Vector Shedding
CHMP/ICH/469991/06	General principles to address the risk of inadvertent germline integration of gene therapy

Concluding remarks

- **Scientific guidance for GTMPs is available and is constantly evolving.**
- **However, guidance/requirements have to be adjusted to the specificity of each individual GTMP.**

→ **Early and constant interaction with regulatory authorities is important for sucessful development of GTMP**

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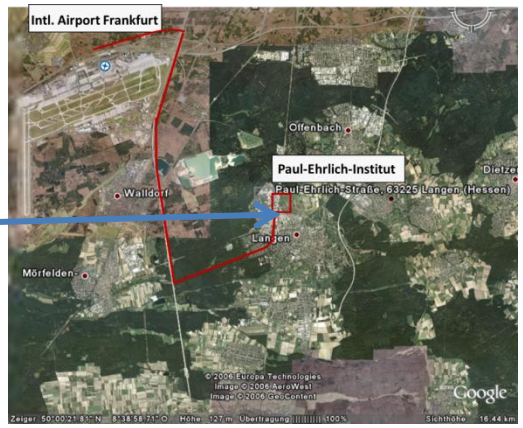

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Thank you !

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