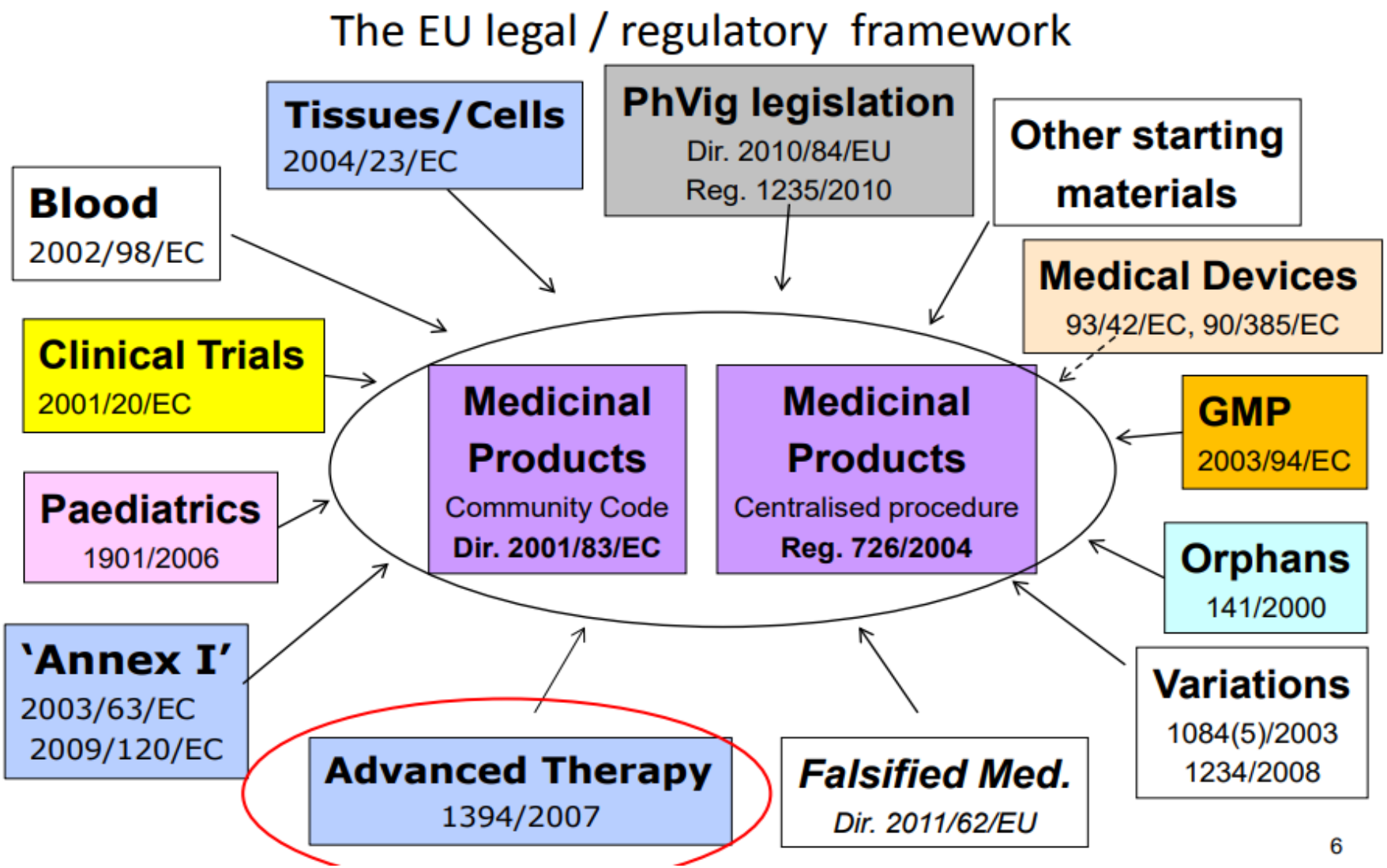


https://www.ema.europa.eu/en/documents/presentation/presentation-introduction-regulatory-up

European Court of Justice Ruling on genome editing

Tue, 14 Aug 2018

Genome editing constitutes genetic modification not covered by the mutagenesis exemption

Marketing authorization applications / CAT 2009-2016 (September)

	2009	2010	2011	2012	2013	2014	2015	2016	Total	Approved
Submitted	3	1	2	3	2	2	1	1	**15**	**8**
GTMP	2	1				2	1	1	6	2
SCTMP				1					1	1
TEP	1		2	2	1	1			7	3
Variations	0	0	1	1	9	4	3	4	22	

Approved: **ChondroCelect** for cartilage repair, 2009 *(withdrawn 06/2016)

MACI for cartilage repair, 2012 *(closure of EU manufacturing site 09/2014)

Glybera for treatment of LPL deficiency, 2013

Provenge for treatment of advanced prostate cancer, 2013 *(withdrawn 05/2015)

Holoclar for treatment of limbal stem cell deficiency, 2015

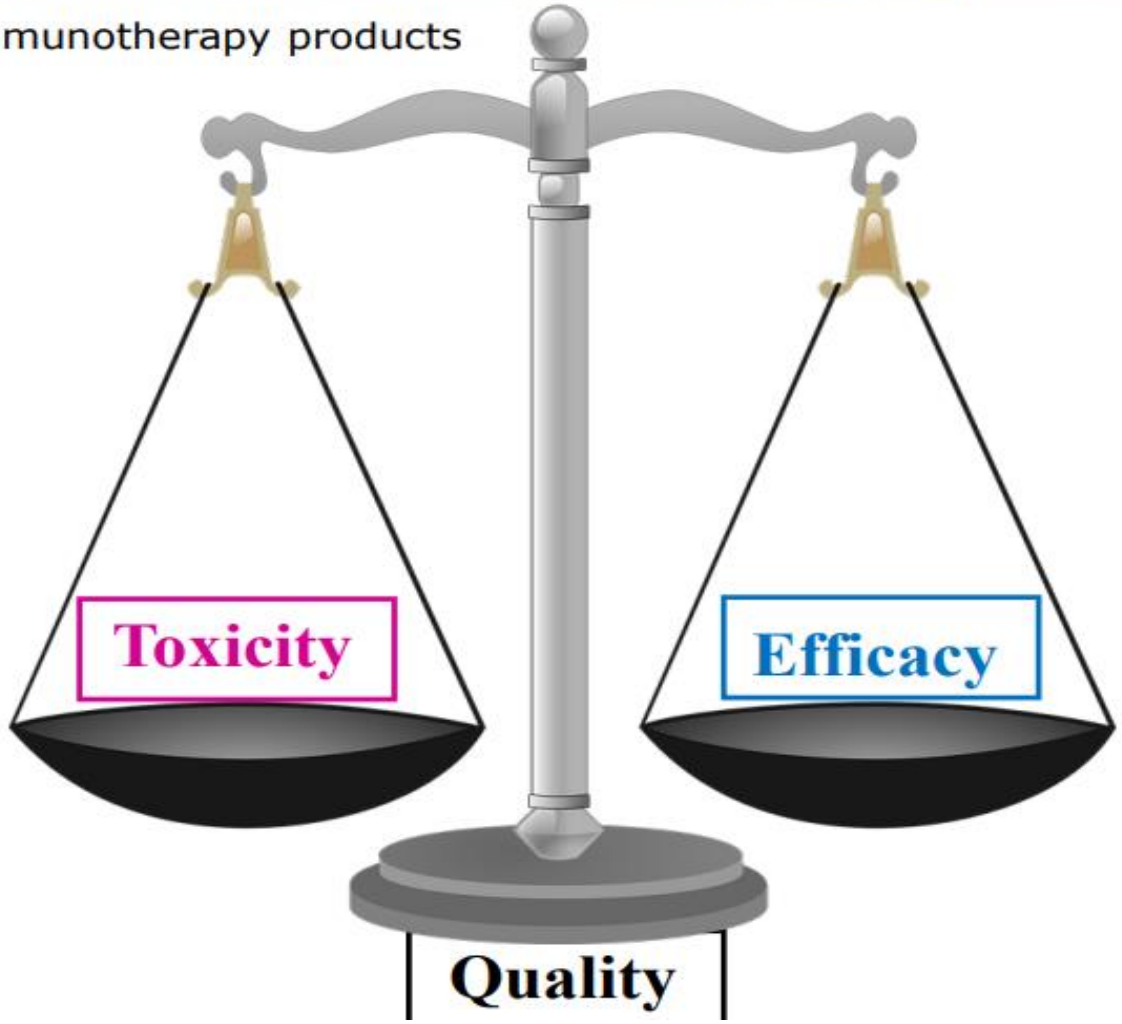
Imlygic for treatment of advanced melanoma, 2015

Strimvelis for treament of ADA-SCID, 2016

Zalmoxis for treatment of high-risk haematological malignancies (adjunctive to HSCT)

✓ 2 ATMPs under evaluation, several new ones expected 2017

Cancer immunotherapy products



2001 83 definitie & klasse

4. Immunological medicinal product: Any medicinal product consisting of vaccines, toxins, serums or allergen products:

(a) vaccines, toxins and serums shall cover in particular:

(i) agents used to produce active immunity, such as cholera vaccine, BCG, polio vaccines, smallpox vaccine;

(ii) agents used to diagnose the state of immunity, including in particular tuberculin and tuberculin PPD, toxins for the Schick and Dick Tests, brucellin;

(iii) agents used to produce passive immunity, such as diphtheria antitoxin, anti-smallpox globulin, antilymphocytic globulin;

(b) "allergen product" shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent.

5. Homeopathic medicinal product: Any medicinal product prepared from products, substances or compositions called homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European

2001 20 clinical trials

6. Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.

2001 18 milieu/uitstoot

D. Conclusions on the potential environmental impact from the release or the placing on the market of GMOs

On the basis of an e.r.a. carried out in accordance with the principles and methodology outlined in sections B and C, information on the points listed in sections D1 or D2 should be included, as appropriate, in notifications with a view to assisting in drawing conclusions on the potential environmental impact from the release or the placing on the market of GMOs:

D.1. In the case of GMOs other than higher plants

1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s).

2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realised under the conditions of the proposed release(s).

3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species.

4. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO and target organisms (if applicable).

5. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO with non-target organisms, including impact on population levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens.

6. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release(s).

7. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any product derived from it, if it is intended to be used as animal feed.

8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s).

2020 1043 uitzonderingen

Article 1

For the purposes of this Regulation, the following definitions apply:

(1) 'clinical trial' means clinical trial as defined in point (a) of Article 2 of Directive 2001/20/EC;

(2) 'sponsor' means sponsor as defined in point (e) of Article 2 of Directive 2001/20/EC;

(3) 'investigational medicinal product' means investigational medicinal product as defined in point (d) of Article 2 of Directive 2001/20/EC;

(4) 'medicinal product' means medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC;

(5) 'genetically modified organism' or 'GMO' means genetically modified organism as defined in point (2) of Article 2 of Directive 2001/18/EC.

Article 2

1. All operations related to the conduct of clinical trials, including packaging and labelling, storage, transport, destruction, disposal, distribution, supply, administration or use of investigational medicinal products for human use containing or consisting of GMOs intended to treat or prevent COVID-19, with the exception of the manufacturing of the investigational medicinal products, shall not require a prior environmental risk assessment or consent in accordance with Articles 6 to 11 of Directive 2001/18/EC or Articles 4 to 13 of Directive 2009/41/EC when these operations relate to the conduct of a clinical trial authorised in accordance with Directive 2001/20/EC.

2. Sponsors shall implement appropriate measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the investigational medicinal product into the environment.

3. By way of derogation from point (a) of Article 6(2) of Regulation (EC) No 726/2004 and from the second indent of the fourth paragraph of point 1.6 of Part I of Annex I to Directive 2001/83/EC, in applications for marketing authorisation for medicinal products containing or consisting of GMOs intended to treat or prevent COVID-19, the applicant shall not be required to include a copy of the competent authority's written consent to the deliberate release into the environment of GMOs for research and development purposes in accordance with Part B of Directive 2001/18/EC.

2003 63

This Annex is divided in four different parts:

- Part I describes the application format, the summary of product characteristics, the labelling, the leaflet and presentation requirements for standard applications (Modules 1 to 5).

- Part II provides derogation for "Specific applications", i.e. well-established medicinal use, essentially similar products, fixed combinations, similar biological products, exceptional circumstances and mixed applications (part bibliographic and part own studies).

- Part III deals with "Particular application requirements" for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, homeopathic medicinal products, herbal medicinal products and orphan medicinal products.

- Part IV deals with "Advanced therapy medicinal products" and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.

Transfer of genetic material may be carried out by direct injection of the ready-prepared vector to the recipients.

1.2. Specific requirements regarding Module 3

Gene therapy medicinal products include:

- naked nucleic acid

- complex nucleic acid or non viral vectors

- viral vectors

- genetically modified cells

As for other medicinal products, one can identify the three main elements of the manufacturing process, i.e.:

- starting materials: materials from which the active substance is manufactured such as, gene of interest, expression plasmids, cell banks and virus stocks or non viral vector;

- active substance: recombinant vector, virus, naked or complex plasmids, virus producing cells, in vitro genetically modified cells;

- finished medicinal product: active substance formulated in its final immediate container for the intended medical use. Depending on the type of gene therapy medicinal product, the route of administration and conditions of use may necessitate an ex vivo treatment of the cells of the patient (see 1.1.b).

3.2.2. Safety

Safety issues arising from immune response to the medicinal products or to the expressed proteins, immune rejection, immuno-suppression, and breakdown of immuno-isolation devices shall be considered.

Certain advanced gene therapy and somatic cell therapy medicinal products (e.g. xenogeneic cell therapy and certain gene transfer products) may contain replication-competent particles and/or infectious agents. The patient may have to be monitored for the development of possible infections and/or their pathological sequelae during pre- and/or post-authorisation phases; this surveillance may have to be extended to close contacts of the patient including health-care workers.

The risk of contamination with potentially transmissible agents cannot be totally eliminated in the use of certain somatic cell therapy medicinal products and certain gene transfer medicinal products. The risk can be minimised, however, by appropriate measures as described in Module 3.

The measures included in the production process must be complemented with accompanied testing methods, quality control processes and by appropriate surveillance methods that must be described in Module 5.

The use of certain advanced somatic cell therapy medicinal products may have to be limited, temporarily or permanently, to establishments that have documented expertise and facilities for assuring a specific follow up of the safety of the patients. A similar approach may be relevant for certain gene therapy medicinal products that are associated with a potential risk of replication-competent infectious agents.

The long term monitoring aspects for the development of late complications shall also be considered and addressed in the submission, where relevant.

Where appropriate, the applicant has to submit a detailed risk management plan covering clinical and laboratory data of the patient, emerging epidemiological data, and, if relevant, data from archives of tissue samples from the donor and the recipient. Such a system is needed to ensure the traceability of the medicinal product and the rapid response to suspicious patterns of adverse events.

VAMF (2003 63)

2. THE PRINCIPLE OF A VAMF

A VAMF is that part of a vaccine Marketing Authorisation Application (MAA) concerning the active substance, including information on the starting materials and reagents, the production process, specification and routine controls, the stability and the viral safety aspects of a vaccine antigen and will not include information on the formulation process or further downstream production steps (See under 3 – The Content of a VAMF).

For a number of vaccines, the same vaccine antigen is used for formulating monovalent and combined vaccine presentations of a given manufacturer. A classical example is a diphtheria antigen that may be used in a series of vaccines such as D, dT, DT, DTPa, dTPa, DTPaHBV, DTPaHBVIPV, DTPa,HBVIPVHib, DTPa+Hib, DTPaIPV, DTPaIPV+Hib, DTPw, DTPw+Hib, DTPwHBV[1]. The VAMF for any given vaccine antigen could also be the VAMF for all of the combinations it is or will be used in, provided that the same data are applicable to these MAs. Then the VAMF certificate issued by the EMEA to the Applicant, will be valid for all the combinations it was approved for or will be extended.

In accordance with Annex I of Directive 2001/83/EC as amended by Commission Directive 2003/63/EC, a vaccine MAA contains as many VAMFs as there are antigens included in the vaccine. E.g., in application of this principle, a monovalent tetanus vaccine contains one vaccine antigen aimed at preventing a single disease and therefore would have one VAMF; a combined diphtheria-tetanus vaccine contains two distinct vaccine antigens (in this case aimed at preventing two diseases) and the vaccine has therefore two VAMFs. To further illustrate the interpretation of the VAMF principle outlined above, a number of somewhat more complex examples are given in the table below.

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-data-requ

3. THE CONTENT OF A VAMF

A VAMF application submitted by a VAMF Applicant (MA Applicant or MAH) will include an administrative section. Further details of this are provided in the relevant EMEA Procedural Guidance on VAMFs (Guideline on requirements for Vaccine Antigen Master File (VAMF) certification - EMEA/CPMP/BWP/4548/03).

The main body of the submission will consist of the following relevant sections of the MA dossier:

EU CTD (NTA, Vol. 2B, Edition 2001)	
3.2.S1	General information
3.2.S.2	Manufacture
3.2.S.3	Characterisation
3.2.S.4	Control of Drug Substance
3.2.S.5	Reference Standards or Materials
3.2.S.6	Container Closure System
3.2.S.7	Stability
3.2.A.1	Equipment and facilities (as relevant for the S-part)
3.2.A.2	Adventitious agents safety evaluation

It may be useful for both the Applicant and competent authorities if, in the MA dossier, the parts concerned be marked as belonging to a VAMF.

3. Discussion (on the problem statement)

For the development of the guideline, the new legal basis and the provisions in Regulation (EU) 2019/6 will be considered.

The draft Annex II introduces the concept of a VAMF. A VAMF is intended to be a stand-alone part of a MA application dossier for a vaccine, which contains all relevant information on quality concerning each of the active substances that are part of the product.

The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or MA holder. The use of a VAMF is optional.

For vaccines containing new vaccine antigen(s) where no VAMF already exists, the applicant shall submit to the Agency a full MA application dossier including all the VAMFs corresponding to each single vaccine antigen for which the use of a VAMF is intended.

IWP discussed if the text in the Annex II would provide sufficient detail about the data requirements to be submitted in support of a VAMF. Information in a VAMF is requested on Part 1 (Summary of the dossier) and Part 2 (Quality documentation), except for Part 2.E (Control tests on the finished product). References are included to standard requirements described in Section IIIb of Annex II.

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-concept-paper-develop

1234/2008 → 2013XC0802

a) **First-time inclusion of a new Vaccine Antigen Master File**			**II**
b) **Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished product**		**1, 2, 3, 4**	**IB**
c) **Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product**	**1**	**1, 2, 3, 4**	**IA_{IN}**

Conditions

1. The updated or amended Vaccine Antigen Master File has been granted a certificate of compliance with legislation of the Union in accordance with Annex I to Directive 2001/83/EC.

Documentation

1. Declaration that the VAMF Certificate and Evaluation Report are fully applicable for the authorised product, VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the MAH (where the MAH is different to the VAMF holder), the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this Marketing Authorisation.
2. VAMF Certificate and Evaluation Report.
3. An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished products including product specific risk assessments.
4. The variation application form should clearly outline the 'present' and 'proposed' VAMF EMA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other VAMFs to which the medicinal product refers even if they are not the subject of the application.

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52013XC0802%

1394/2007 (ATMP)

SUBJECT MATTER AND DEFINITIONS

Article 1

Subject matter

This Regulation lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products.

Article 2

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

gene therapy

5. A product which may fall within the definition of:

— a somatic cell therapy medicinal product or a tissue engineered product, and

— a gene therapy medicinal product,

shall be considered as a gene therapy medicinal product.

CHAPTER 2
MARKETING AUTHORISATION REQUIREMENTS

Article 3

Donation, procurement and testing

Where an advanced therapy medicinal product contains human cells or tissues, the donation, procurement and testing of those cells or tissues shall be made in accordance with Directive 2004/23/EC.

Article 4

Clinical trials

1. The rules set out in Article 6(7) and Article 9(4) and (6) of Directive 2001/20/EC in respect of gene therapy and somatic cell therapy medicinal products shall apply to tissue engineered products.

2. The Commission shall, after consulting the Agency, draw up detailed guidelines on good clinical practice specific to advanced therapy medicinal products.

Article 5

Good manufacturing practice

The Commission shall, after consulting the Agency, draw up guidelines in line with the principles of good manufacturing practice and specific to advanced therapy medicinal products.

2009 120

2. DEFINITIONS

For the purposes of this Annex, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.

2.1. 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.

3.2. Specific requirements for gene therapy medicinal products

3.2.1. *Introduction: finished product, active substance and starting materials*

3.2.1.1. Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)

The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

4.2. Specific requirements for gene therapy medicinal products

In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.

4.2.1. *Pharmacology*

(a) *In vitro* and *in vivo* studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic "proof of concept" studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.

(b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of functionality and activity in target cells and tissues shall be provided.

4.2.2. *Pharmacokinetics*

(a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.

(b) Investigations of shedding and risk of transmission to third parties shall be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

4.2.3. *Toxicology*

(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the *in vivo* effect of expressed nucleic acid sequence-related products which are not intended for the physiological function shall be evaluated.

(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.

(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.

(d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.

(e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant *in vivo*/*in vitro* models.

(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.

(g) *Additional toxicity studies*

— Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be performed, if biodistribution data indicate a risk for germline transmission.

— Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.

5.2. Specific requirements for gene therapy medicinal products

5.2.1. *Human pharmacokinetic studies*

Human pharmacokinetic studies shall include the following aspects:

(a) shedding studies to address the excretion of the gene therapy medicinal products;

(b) biodistribution studies;

(c) pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).

5.2.2. *Human pharmacodynamic studies*

Human pharmacodynamic studies shall address the expression and function of the nucleic acid sequence following administration of the gene therapy medicinal product.

5.2.3. *Safety studies*

Safety studies shall address the following aspects:

(a) emergence of replication competent vector;

(b) emergence of new strains;

(c) reassortment of existing genomic sequences;

(d) neoplastic proliferation due to insertional mutagenicity.

2.1.1. Gene therapy medicinal product

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

[3] Taking into account the remit of the European Medicines Agency, as stated in Article 17 of Regulation 1394/2007 i.e. "Any applicant developing a product based on genes, cells or tissues may request a scientific recommendation of the Agency with a view to determining whether the referred product falls, on scientific grounds, within the definition of an advanced therapy medicinal product ...."

[4] The complete list of scientific recommendations on classification of ATMPS can be found at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac05800862c0

(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.

It should be noted that in order to be considered a gene therapy medicinal product, both the characteristics (a) and (b) have to be fulfilled.

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-adv

2.2. Scientific principles applied to the classification of ATMPs

According to Article 17 of the ATMP Regulation, products are classified according to the respective definitions of gene therapy medicinal product, somatic cell therapy medicinal products, tissue engineered product and combined ATMP, on the basis of scientific information provided by the applicant.

This section elucidates the scientific criteria applied for the classification of ATMPs. The following list of criteria is based largely on the experience gained by the CAT through recommendations on ATMP classification issued so far[4]. These should not be considered as exhaustive and might be subject to change as science evolves.

2.2.3. Criteria for GTMP

The definition of gene therapy medicinal product according to Annex I, part IV, section 2.1 of Directive 2001/83/EC, as amended, is articulated into two conditions that have both to be fulfilled simultaneously: 1) the product has to be a biological medicinal product[iv] and contains recombinant nucleic acid(s) and 2) the recombinant nucleic acid(s) should be directly involved in the mechanism of action (and hence therapeutic action of the product. In this respect the following observations can be made:

- Indent (a) of the definition of Gene therapy medicinal product:

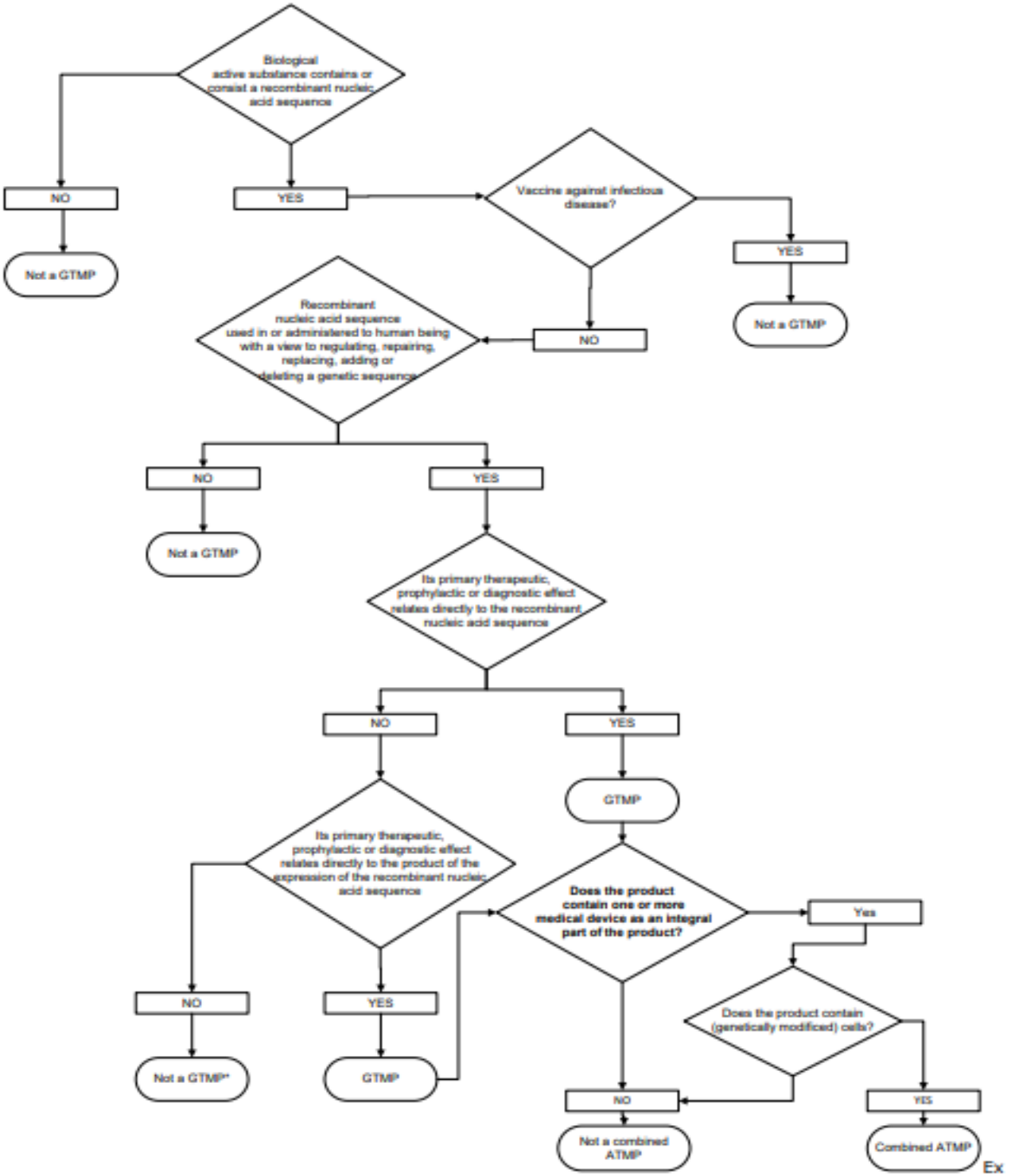
  the recombinant nucleic acids should be of biological origin independently from the origin of the vector system used (e.g. viral/bacterial vectors or micellar and liposomal formulations, etc.)

- Indent (b) of the definition of Gene therapy medicinal product :

  "***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***": the MoA and proposed indication, as claimed by the applicant are of essential to assess if there is a "direct" relationship between the therapeutic, prophylactic or diagnostic effect of the product and the delivered genetic sequence or the expressed product. As an illustration, the CAT provided two scientific recommendations for classifications for genetically modified T cells encoding an exogenous thymidine kinase gene. The T cell preparations were intended for immune reconstitution as adjunct treatment in haematopoietic stem cell transplantation.

- The legislation provides that ***"Gene therapy medicinal products shall not include vaccines against infectious diseases"***. For classification purposes, vaccines are expected to have prophylactic mode of action, i.e. prevention of an infectious disease in humans. If a product is intended to treat pathologies caused by the infection (e.g. malignancies), it is classified as a GTMP. Live recombinant viral vectors (delivering genes encoding specific antigen sequences into human somatic cells) could fulfil the definition of Gene Therapy Medicinal Products (GTMP) when administered for example in

oncology, but similar products would not be classified GTMPs when intended as prophylactic against infectious disease. In order to enable the classification of borderline products (treatment of infections or premalignancies) the therapeutic indication and target population should be clearly defined.



Explanatory notes: *) The product can contain genetically modified cells for which specific requirements should be followed (see 'Guideline on

CAT 8-10 dec 2021

7.2. Coordination with EMA Scientific Committees

7.2.1. Extension of indication of approved ATMPs: additional 1-year protection period

Scope: Presentation on the regulatory aspects

Action: for information

Topic postponed until the January 2022 meeting.

7.3.3. Reflection paper on criteria to be considered for the evaluation of new active substance (NAS) status of biological substances

EMA: Veronika Jekerle (on behalf of the drafting group)

Scope: feedback on the status of the NAS reflection paper

Action: for information

EMA provided detailed information on status of the reflection since it was discussed at the CAT in July 2021. The document underwent regulatory and legal scrutiny by both EMA regulatory and legal affairs offices, and by the Commission. This was a necessary step with regards to the regulatory nature of the NAS status. EMA informed CAT members that the European Commission shared EMA's view that this is an important document in view of its regulatory implications, which go beyond purely scientific assessment. All documents and comments received are made available to the BWP-CAT drafting group and to all CAT and BWP members.

This topic was included in the agenda on specific request from CAT members to be informed on the grounds for delays in the finalisation of this CAT 2021 work plan topic. During the preparation of the December CAT agenda, EMA considered that this topic was not mature enough to bring back to the CAT: the BWP-CAT drafting group has to review all the comments and finalise the draft reflection paper. It was considered more

appropriate to present the revised draft reflection paper to CAT for discussion and adoption early 2022, once finalised by the drafting Group.

The European Commission representative summarised the legal issues that they have identified during the review.

The CAT chair thanked EMA for the information provided and asked for a more proactive communication to CAT on CAT work plan topics and legal/regulatory considerations relevant to ATMPs.

As the comments from the external consultation will have to be reviewed in 2022, it was agreed to include the NAS reflection paper in the CAT work plan for 2022 (see 7.6.2).

8. Any other business

8.1.1. CAT Learnings

CAT: Martina Schüssler-Lenz

Scope: CAT learnings on Insertional mutagenesis and germline transmission risk analysis in the context of genome editing

Action: for discussion

CAT discussed following topics: Duration of follow-up (see 7.8.3), insertional mutagenesis, germline integration for genome editing (GE) products.

On the need to include genome editing in the ICH S12 Biodistribution guideline, CAT agreed with the position from the EU Rapporteurs (Rune Kjeken, Claire Beuneu) that germline integration for GE should not be specifically mentioned: the general principle apply also for GE products.

On the topics: duration of follow-up and insertional mutagenesis, CAT members will develop a discussion paper to facilitate the CAT discussions.

Date of next CAT meeting:

19 – 21/01/2022

The active substance is presented as four ***in vitro*** transcribed mRNA molecules each encoding one tumour antigen.

Brief description of the finished product

Drug product consists of the four individual drug substances in a liposomal formulation.

Proposed indication

Treatment of malignant melanoma.

EMA/CAT conclusion

The procedure was finalised on 20 July 2018 for the following recommendation.

On the basis that:

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

- the product contains an active substance that consists of recombinant nucleic acid molecules of biologic origin, namely the coding sequence of four tumour antigens;
- the product is intended to be administered to human beings with a view to adding a genetic sequence;
- its therapeutic effect relates directly to the product of genetic expression of this sequence,

the EMA/CAT considers that the product falls within the definition of a gene therapy medicinal product, as provided in Article 2(1) of Regulation (EC) 1394/2007.

Brief description (or name when available) of the active substance(s)

In vitro transcribed mRNA sequences encoding six non-small cell lung cancer (NSCLC) associated antigens.

Brief description of the finished product

Powder and solvent for solution for injection.

Proposed indication

Treatment of non-small cell lung cancer.

EMA/CAT conclusion

The procedure was finalised on 27 January 2017 for the following recommendation.

On the basis that the product:

30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

- contains an active substance that consist of a set of different recombinant nucleic acid molecules of biologic origin, namely the coding sequences of the human NSCLC associated antigens;
- is intended to be administered to human beings with a view to adding genetic sequences;
- its therapeutic effect relates directly to the product of genetic expression of these sequences,

the EMA/CAT considers that the Product falls within the definition of a gene therapy medicinal product as provided in Article 2(1) of Regulation (EC) 1394/2007.

Genetically modified adenovirus coding for human granulocyte-macrophage colony stimulating factor (GM-CSF)

Brief description of the finished product

Concentrate for solution for injection

Proposed indication

Treatment of cancer

EMA/CAT conclusion

On the basis that:

- The product contains a biological medicinal product as the active substance;
- The active substance is a recombinant nucleic acid administered to human beings with a view to adding a genetic sequence;
- Its therapeutic effect relates directly to the product of the genetic expression of this sequence

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the EMA/CAT considers that the Product falls within the definition of a gene therapy medicinal product.

https://www.ema.europa.eu/en/documents/report/scientific-recommendation-classification-advan

Prevention and Treatment of hepatitis C (HCV) and HCV-induced hepatocellular carcinoma

EMA/CAT comment

Consideration of Article 1(2) of Directive 2001/83/EC

The product consist of an adenoviral vector derived from subgroup C chimpanzee adenovirus ChAd3 expressing the Non structural region (NS3, NS4A, NS4B, NS5A and NS5B) of hepatitis C virus (HCV), can be considered as a "substance" in the meaning of the pharmaceutical legislation (in accordance

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with article 1(3) of the Directive 2001/83/EC), which is administered to humans with a view to restoring physiological functions.

The product is presenting as having properties for treating a disease in human beings: Prevention and treatment of hepatitis C (HCV) and HCV-induced hepatocellular carcinoma

According to Article 1(2), the restoration, correction or modification of the physiological function is to be mediated by the substances that exert "a pharmacological, immunological or metabolic action".

AdCh3NSmut1 fulfil the conditions expressed in the article 1(2) of Directive 2001/83/EC, as it is presented as acting via immunological means.

Based on the above considerations, it is considered that AdCh3NSmut1 falls within the definition of a medicinal product

https://www.ema.europa.eu/en/documents/report/scientific-recommendation-adva

treatment of hepatitis C (HCV) and HCV-induced hepatocellular carcinoma

According to Article 1(2), the restoration, correction or modification of the physiological function is to be mediated by the substances that exert "a pharmacological, immunological or metabolic action".

AdCh3NSmut1 fulfil the conditions expressed in the article 1(2) of Directive 2001/83/EC, as it is presented as acting via immunological means.

Based on the above considerations, it is considered that AdCh3NSmut1 falls within the definition of a medicinal product

Fulfilment of Article 2(1) of Regulation (EC) No 1394/2007

The product is a vectored vaccine against hepatitis C virus (HCV). The mechanism of action is based on the induction of a potent T-cell immune response against the non-structural proteins of the HCV virus.
The product is intended to be administered prophylactically to the patient in view of preventing or treating HCV infection as well as HCV- induced hepatocellular carcinoma
Based on the above considerations, it is considered that it is a vaccine administered to the patient to prevent and/or to treat an infectious disease.

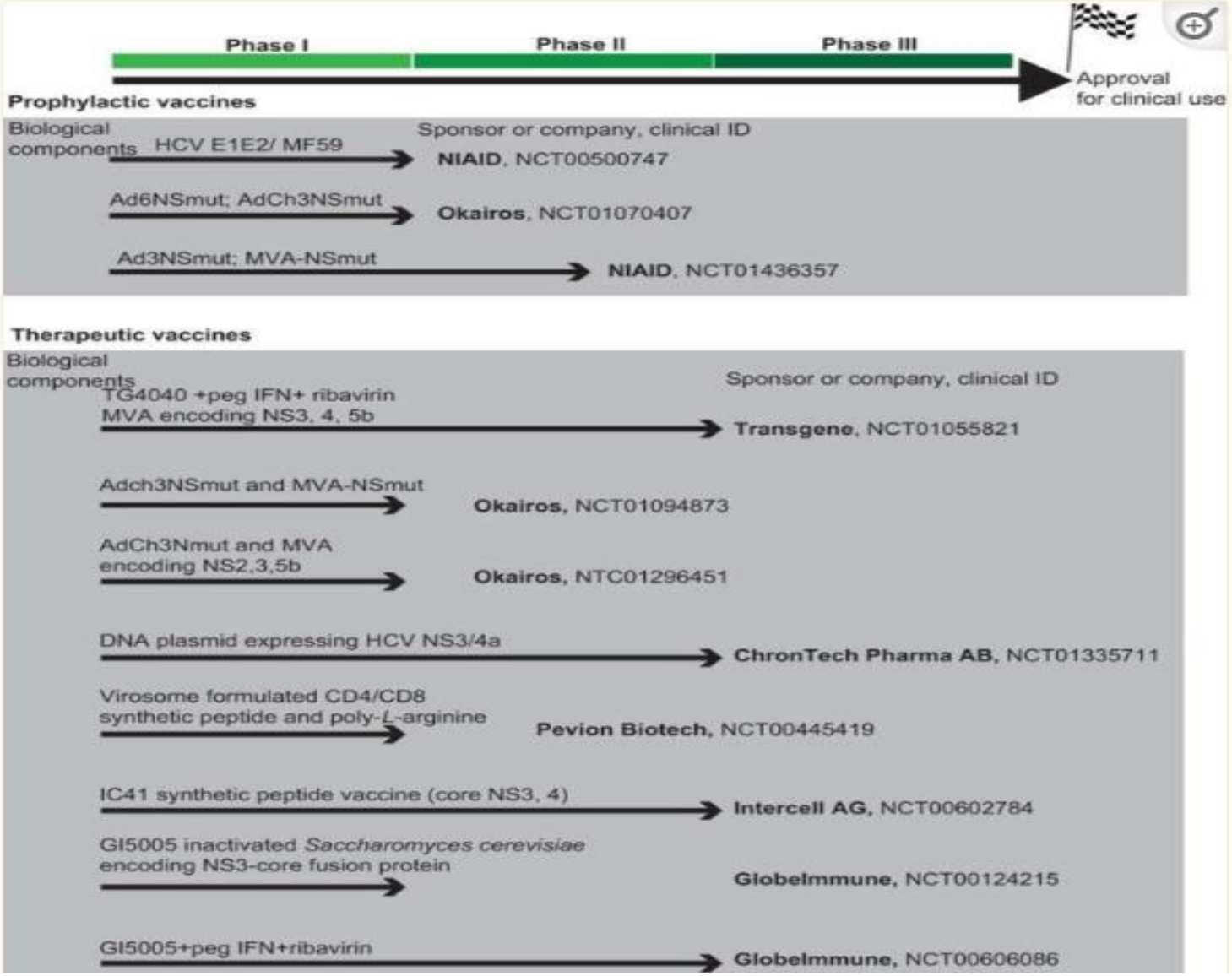
With reference to Section 2.1 of Part IV of Annex I to Directive 2001/83/EC, which stipulates that gene therapy medicinal products shall not include vaccines against infectious disease, the product does therefore not fall within the definition of an advanced therapy medicinal product as provided in Article 2(1)(a) of Regulation (EC) No 1394/2007.

EMA/CAT conclusion

On the basis of that,

With reference to Section 2.1 of Part IV of Annex I to Directive 2001/83/EC, which stipulates that gene therapy medicinal products shall not include vaccines against infectious disease, the EMA/CAT considers that the product does not fall within the definition of an advanced therapy medicinal product as provided in the article 2(1)(a) of the Regulation (EC) No 1394/2007.

There are two major approaches to HCV for vaccine development. One is prophylactic and the other is therapeutic vaccines for clinical use (figure 2).



Study of a New MVA Vaccine for Hepatitis C Virus

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT01296451

Recruitment Status : Completed
First Posted : February 15, 2011
Last Update Posted : April 26, 2016

Sponsor:
ReiThera Srl

Collaborators:
University of Oxford
Oxford University Hospitals NHS Trust
University Hospital Birmingham

Information provided by (Responsible Party):
ReiThera Srl

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Go to

Brief Summary:

The study is aimed at assessing the safety of AdCh3NSmut and the new candidate vaccine MVA-NSmut when administered sequentially, or alone, to healthy volunteers and patients with hepatitis C virus infection The study also aims at assessing the cellular immune respon generated by AdCh3NSmut and MVA-NSmut administered as mentioned above.

STEFANO COLLOCA

Chief Of Technology

Stefano was one of founders and the Director of Viral Vector Department at Okairos Srl. Previously, Stefano was Senior Research Fellow at IRBM, where he contributed to drug discovery programs on the hepatitis B and C viruses; and to the adenovirus vector development for therapeutic gene transfer and gene-based vaccination.

Stefano has strong research experience in the field of viral vectors for gene delivery and expertise in good manufacturing process (GMP) production and quality assessment.

Stefano has overseen and directed manufacturing campaigns of numerous GMP clinical trial materials, and is responsible for the GMP Facility at ReiThera. He has published articles in leading journals such as New England Journal of Medicine and Nature Medicine on viral and infection and vaccines.

As with any other vaccine, Guillan-Barre syndrome (GBS) or immune mediated reactions that can lead to organ damage can occur. However, such problems are very rare events with any vaccine and have never occurred with AdCh3 vector vaccines to date.

As with any other vaccine, serious allergic reactions including anaphylaxis can occur. Volunteers will be vaccinated in a clinical area where Advanced Life Support drugs and equipment are immediately available for the management of serious adverse reactions.

Indirect effects: There is no theoretical basis for the possibility that exposure to NSmut as a result of this vaccination would lead to any deleterious effect on any future treatment for Hepatitis C in an individual.

The genetic modification of AdCh3 leading to expression of NSmut is unlikely to lead to any deleterious events in the event of this gene being transferred to other viruses. NSmut has a mutation inactivating the enzymatic activity of the encoded polymerase gene eliminating any potential replicative capacity of the insert.

If AdCh3NSmut1 re-acquired the ability to replicate reliably the consequences would likely be minimal, with local antibody responses likely adequate to suppress any infection. Adenoviruses in humans rarely cause serious illness, although they commonly are associated with upper respiratory tract infections and less commonly gastrointestinal, ophthalmic, genitourinary and neurological disease

Step 3 – Evaluation of the likelihood of adverse effects

Ongoing and completed Phase I trials in Oxford include those using the AdCh3 and Ad6 vectors encoding the NS antigen (AdCh3NSmut and Ad6NSmut) in healthy volunteers (study HCV001), in HCV infected patients (study HCV002TV), and study HCV003 which is also assessing the safety and immunogenicity of AdCh3NSmut1 – identical to the AdCh3NS to be used in this study – and MVA-NSmut in healthy volunteers.

Review

Adenoviruses as vaccine vectors

Nia Tatsis, Hildegund C.J. Ertl

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https://doi.org/10.1016/j.ymthe.2004.07.013

Adenoviruses have transitioned from tools for gene replacement therapy to bona fide vaccine delivery vehicles. They are attractive vaccine vectors as they induce both innate and adaptive immune responses in mammalian hosts. Currently, adenovirus vectors are being tested as subunit vaccine systems for numerous infectious agents ranging from malaria to HIV-1. Additionally, they are being explored as vaccines against a multitude of tumor-associated antigens. In this review we describe the molecular biology of adenoviruses as well as ways the adenovirus vectors can be manipulated to enhance their efficacy as vaccine carriers. We describe methods of evaluating immune responses to transgene products expressed by adenoviral vectors and discuss data on adenoviral vaccines to a selected number of pathogens. Last, we comment on the limitations of using human adenoviral vectors and provide alternatives to circumvent these problems. This field is growing at an exciting and rapid pace, thus we have limited our scope to the use of adenoviral vectors as vaccines against viral pathogens.

Introduction

Traditional viral vaccines are based on inactivated or attenuated pathogens. Advances in molecular virology in concert with viral immunology now allow for the genetic engineering of vectors expressing solely those viral antigens that induce immune correlates of protection. Adenoviruses were initially vectored as vehicles for gene therapy. Attempts to replace missing or faulty genes by adenoviral gene transfer were largely unsuccessful in experimental animals and human volunteers alike due to innate and adaptive immune responses induced by the adenoviral antigens. While this reduced their appeal as gene replacement vehicles it invited their use as vaccine carriers. Adenoviral vectors are attractive candidates for transfer of foreign genes for a number of reasons. The adenoviral genome is well characterized and comparatively easy to manipulate. Most adenoviruses cause mild diseases in immunocompetent human adults and by deletion of crucial regions of the viral genome the vectors can be rendered replication-defective, which increases their predictability and reduces unwanted side effects. Adenoviruses have a broad tropism infecting a variety of dividing and nondividing cells. They can be grown to high titers in tissue culture. They can be applied systemically as well as through mucosal surfaces and their relative thermostability facilitates their clinical use.

Thus far most efforts have focused on vectors derived from adenovirus of the human serotype 5 (AdHu5) for eventual use as vaccines for humans, while bovine, porcine, and ovine adenoviruses have been explored for veterinary use.

Human Gene Therapy, Vol. 25, No. 4 | Reviews

Adenovirus-Based Vaccines for Fighting Infectious Diseases and Cancer: Progress in the Field

Dragomira Majhen ✉, Hugo Calderon, Naresh Chandra, Carlos Alberto Fajardo, Anandi Rajan, Ramon Alemany, and Jerome Custers

Published Online: 28 Feb 2014 | https://doi.org/10.1089/hum.2013.235

Abstract

The field of adenovirology is undergoing rapid change in response to increasing appreciation of the potential advantages of adenoviruses as the basis for new vaccines and as vectors for gene and cancer therapy. Substantial knowledge and understanding of adenoviruses at a molecular level has made their manipulation for use as vaccines and therapeutics relatively straightforward in comparison with other viral vectors. In this review we summarize the structure and life cycle of the adenovirus and focus on the use of adenovirus-based vectors in vaccines against infectious diseases and cancers. Strategies to overcome the problem of preexisting antiadenovirus immunity, which can hamper the immunogenicity of adenovirus-based vaccines, are discussed. When armed with tumor-associated antigens, replication-deficient and oncolytic adenoviruses can efficiently activate an antitumor immune response. We present concepts on how to use adenoviruses as therapeutic cancer vaccines and consider some of the strategies used to further improve antitumor immune responses. Studies that explore the prospect of adenoviruses as vaccines against infectious diseases and cancer are underway, and here we give an overview of the latest developments.

As of April 21, 2022, at least 169 cases of acute hepatitis in children have been reported in the WHO European Region and the Americas.

Furthermore, the WHO confirmed seventeen children (one month to 16 years old) had required liver transplantation.

And at least one fatality has been reported.

Cases have been reported in the United Kingdom of Great Britain and Northern Ireland (114), Spain (13), Israel (12), the United States of America (9), Denmark (6), Ireland (<5), The Netherlands (4), Italy (4), Norway (2), France (2), Romania (1), and Belgium (1).

'It is not yet clear if there has been an increase in hepatitis cases or an increase in awareness of hepatitis cases that occur at the expected rate but go undetected,' wrote the WHO on April 23, 2022.

The clinical syndrome among identified cases is acute hepatitis (liver inflammation) with markedly elevated liver enzymes.

The common viruses that cause acute viral hepatitis (hepatitis viruses A, B, C, D, and E) have not been detected in any of these cases.

While adenovirus is a possible hypothesis, investigations are ongoing for the causative

Adenovirus was detected in at least 74 cases, and 18 have been identified as F type 41. And the SARS-CoV-2 coronavirus was identified in 20 cases.

Furthermore, there have been 19 children detected with a SARS-CoV-2 and adenovirus co-infection.

The United Kingdom, where most cases have been reported, has recently observed a significant increase in adenovirus infections in the community following low circulation levels earlier in the COVID-19 pandemic.

The Netherlands also reported concurrent increasing community adenovirus circulation.

While adenovirus is currently one hypothesis as the underlying cause, it does not fully explain the severity of the clinical picture.

Adenovirus-based tuberculosis vaccine

There is only one clinically approved tuberculosis vaccine namely Bacillus Calmette Guerin (BCG); however, this vaccine cannot protect against pulmonary tuberculosis. AdHu5 is the most commonly used human adenovirus serotype for the development of the tuberculosis vaccine.

The most widely studied adenovirus-based tuberculosis vaccine is E1/E2 depleted AdHu5 vector expressing immunodominant *Mycobacterium tuberculosis* antigen 85A, and the expression is controlled by the cytomegalovirus promoter.

Background

Recombinant adenovirus-vectored (Ad) tuberculosis (TB) vaccine platform has demonstrated great potential to be used either as a stand-alone or a boost vaccine in murine models. However, Ad TB vaccine remains to be evaluated in a more relevant and sensitive guinea pig model of pulmonary TB. Many vaccine candidates shown to be effective in murine models have subsequently failed to pass the test in guinea pig models.

Methods and Findings

Specific pathogen-free guinea pigs were immunized with BCG, AdAg85A intranasally (i.n), AdAg85A intramuscularly (i.m), BCG boosted with AdAg85A i.n, BCG boosted with AdAg85A i.m, or treated only with saline. The animals were then infected by a low-dose aerosol of *M. tuberculosis* (*M.tb*). At the specified times, the animals were sacrificed and the levels of infection in the lung and spleen were assessed. In separate studies, the long-term disease outcome of infected animals was monitored until the termination of this study. Immunization with Ad vaccine alone had minimal beneficial effects. Immunization with BCG alone and BCG prime-Ad vaccine boost regimens significantly reduced the level of *M.tb* infection in the tissues to a similar extent. However, while BCG alone prolonged the survival of infected guinea pigs, the majority of BCG-immunized animals succumbed by 53 weeks post-*M.tb* challenge. In contrast, intranasal or intramuscular Ad vaccine boosting of BCG-primed animals markedly improved the survival rate with 60% of BCG/Ad i.n- and 40% of BCG/Ad i.m-immunized guinea pigs still surviving by 74 weeks post-aerosol challenge.

PLoS One

Onderzoek naar TBC-vaccin tegen corona onder zorgmedewerkers

Datum bericht: 26 maart 2020

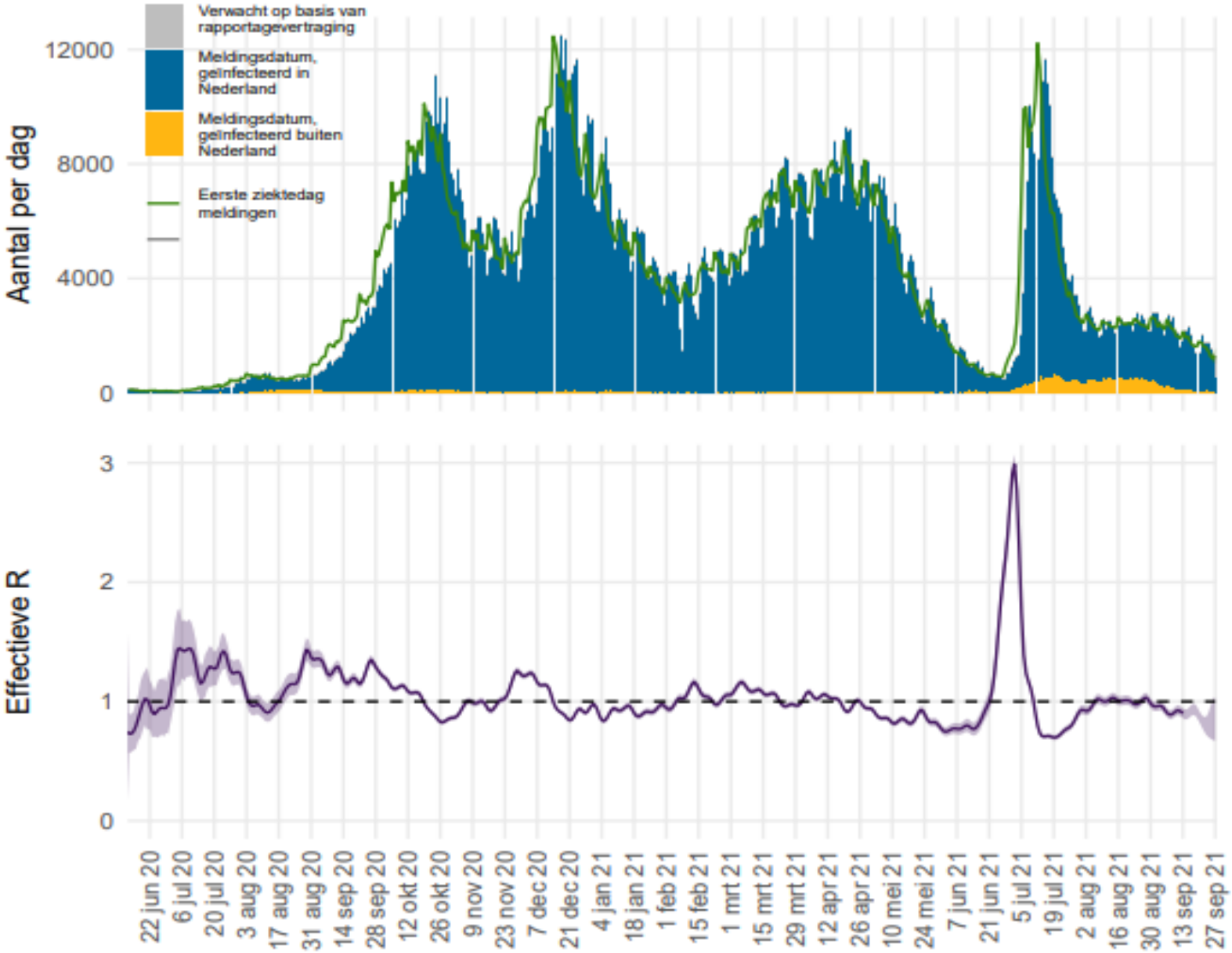
Het Radboudumc en het UMC Utrecht gaan onderzoeken of zorgmedewerkers beter beschermd zijn tegen het coronavirus na een vaccinatie tegen tuberculose (BCG-vaccin). Dit vaccin beschermt niet direct tegen het coronavirus, maar geeft de afweer een boost waardoor mogelijk een betere bescherming tegen het coronavirus ontstaat en de infectie milder verloopt.

Uitgaansbeleid

Dansen met Janssen blijkt toch niet zo'n goed plan nu de besmettingen omhoogschieten

Publiek, afgelopen vrijdag, op het Stereo Sunday Festival in Venlo. Beeld ANP

De horeca is de grootste stijger als bron voor nieuwe coronabesmettingen. Direct toegang tot feesten na een vaccinatie wordt elvest



Figuur 29: Het effectieve reproductiegetal R voor Nederland.

Ook in Fryslân is het RS-virus aanwezig bij kinderen, maar de drukte in de Friese ziekenhuizen valt vooralsnog mee

Rosalie Mulder • 28 juli 2021, 09:09 • Regio

Deel dit artikel

Adenovirus vaccine

Adenovirus vaccine is only available for United States military personnel. There is currently no adenovirus vaccine available to the general public.

Adenovirus vaccine contains live adenovirus Type 4 and Type 7. It will prevent most illness caused by these two virus types.

The vaccine comes as two tablets, taken orally (by mouth) at the same time. The tablets should be swallowed whole, not chewed or crushed.

The vaccine is approved for military personnel 17 through 50 years of age. It is recommended by the Department of Defense for military recruits entering basic training. It may also be recommended for other military personnel at high risk for adenovirus infection.

Adenovirus vaccine may be given at the same time as other vaccines.

Adenovirus Type 4 and Type 7 Vaccine Description 2022

Adenovirus Type 4 and Type 7 Vaccine is a live, oral vaccine that contains viable, selected strains of human adenovirus Type 4 and human adenovirus Type 7 prepared in human-diploid fibroblast cell cultures (strain WI-38). The virus strains have not been attenuated.

The cells are grown, and the virus growth is maintained in Dulbecco's Modified Eagle's Medium, fetal bovine serum, and sodium bicarbonate. The virus is harvested, freed of particulate cellular material by filtration, formulated, and dried by lyophilization. The dried virus material includes monosodium glutamate, sucrose, D-mannose, D-fructose, dextrose, human serum albumin, potassium phosphate, and plasdone C.

The U.S. FDA-approved vaccine comprises two tablets (one tablet of Adenovirus Type 4 and one tablet of Adenovirus Type 7) designed to pass intact through the stomach and release the live virus in the intestine. On January 8, 2022, the U.S. CDC updated the Adenovirus VIS.

U.S. FOOD & DRUG ADMINISTRATION

Our STN: BL 125296/82

SUPPLEMENT APPROVAL

Teva Women's Health, Inc.
Attention: Angela Randall
11100 Nall Avenue
Overland Park, KS 66211

October 15, 2019

Dear Ms. Randall:

We have approved your request submitted and received on April 15, 2019, to supplement your Biologics License Application (BLA) under section 351(a) of the Public Health Service Act for Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, manufactured at Barr Laboratories in Forest, VA, (b) (4) to update Section 8 of the package insert (PI) to comply with 21 CFR 201.57(c)(9)(i)-(iii) to address the Pregnancy, Lactation and Labeling Rule, to add Sections 5.3, 6.2 and 13 to the PI, and to revise the HIGHLIGHTS section, as well as Section 17 of the PI.

LABELING

We hereby approve the draft package insert labeling submitted under amendment 4, dated October 10, 2019.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the final content of labeling (21 CFR 601.14) in Structured Product Labeling (SPL) format via the FDA automated drug registration and listing system, (eLIST) as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/

Wat is het adenovirus?

Het adenovirus is een groepsnaam voor tientallen verschillende soorten virussen. In 2015 zijn er ruim 47 verschillende types bekend. Deze virussen zorgen voor verschillende ziekten bij de mens, die vaak lichte symptomen geven. Het virus is voorzien van uitsteeksels die op een speld lijken. De benaming adenovirus is afkomstig van adenoïd oftewel neusamandel. In 1953 werd dit virus namelijk voor het eerst ontdekt in een neusamandel dat verwijderd was bij een kind. Het virus kan zowel bij mensen als bij dieren voorkomen. Mensen worden waarschijnlijk niet ziek van het dierlijke adenovirus. Andersom is wel bekend dat dieren en met name apen ziek kunnen worden van het menselijke adenovirus.

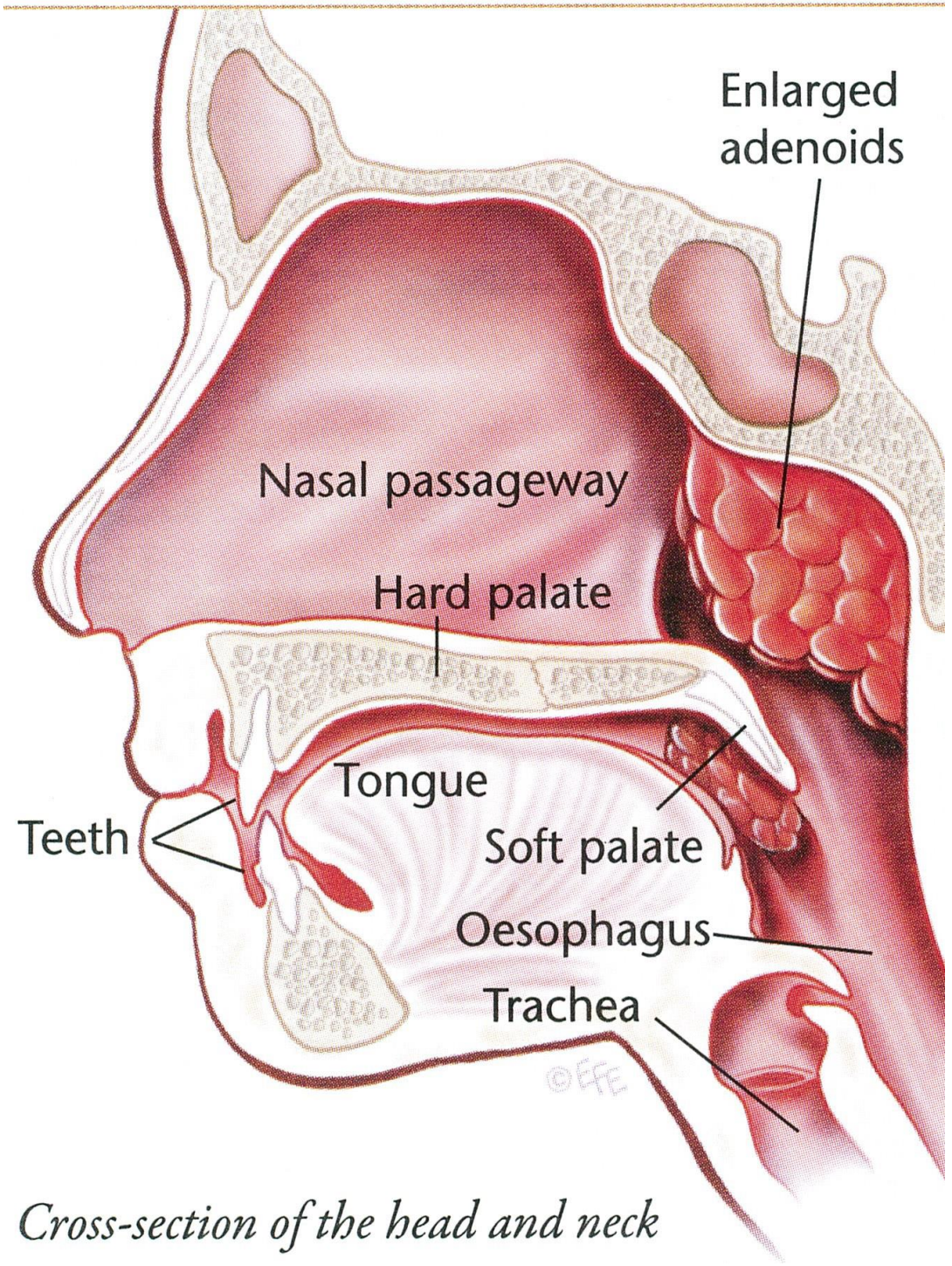
Oog: Slijmvlies-hoornvliesontsteking of bindvliesontsteking

Het adenovirus kan een ontsteking aan het slijmvlies en het hoornvlies veroorzaken (conjunctivitis). Het hoornvlies is het voorste en eerste gedeelte van het oog, het doorzichtige vliesje. Besmetting met het adenovirus kan via de handen plaatsvinden, bijvoorbeeld door het wrijven in de ogen. Deze ontsteking verloopt vaak mild. Ook kan er sprake zijn van een luchtweginfectie, waarna een ontsteking van het hoornvlies ontstaat. Het oog wordt rood en zal een waterige afscheiding vertonen. Er ontstaat een grote overgevoeligheid voor licht. Er is sprake van een slijmvliesontsteking. Het slijmvlies kan gaan zwellen en bloedinkjes vertonen. In veel gevallen zal ook het hoornvlies ontstoken raken. Slechter zien is een veel voorkomende klacht. Behandeling is niet nodig. Soms worden oogdruppels voorgeschreven.

Luchtweginfectie

Vooral bij kinderen worden luchtweginfecties veroorzaakt door het adenovirus. Maar ook volwassenen kunnen hier mee te maken krijgen. De volgende luchtweginfecties kunnen door het adenovirus veroorzaakt worden:

- **Kroep**: ook wel tracheale bronchitis genoemd. De bovenste luchtwegen raken als eerste geïnfecteerd. Er ontstaat een blaffende hoest, heesheid en een vreemd ademgeluid. Ook ontstaat er vaak koorts en het intrekken van de borstkas. Behandeling vindt plaats door het geven van steroïden en soms adrenaline.
- **Bronchitis**: dit is een ontsteking van de bronchiën. De kleine vertakkingen in de longen raken ontstoken. Symptomen zijn een droge hoest en later het ophoesten van slijm. Er treedt vaak koorts op en soms is er sprake van benauwdheid. Behandeling bestaat uit rust, soms stomen en voldoende drinken. De arts kan bekijken of verdere behandeling noodzakelijk is.
- **Longontsteking**: ook longontsteking begint met een verkoudheid, maar gaat niet over. Er ontstaat koorts, spierpijn, pijn tijdens het ademhalen, het ophoesten van groen of geel slijm, benauwdheid en een lusteloos gevoel. Antibiotica werken alleen bij een bacteriële infectie. Het adenovirus is hier tegen bestand



Cross-section of the head and neck

THE JOURNAL OF GENE MEDICINE
J Gene Med 2007; **9**: 910–921.
Published online in Wiley InterScience (www.interscience.wiley.com) **DOI:** 10.1002/jgm.1096

RESEARCH ARTICLE

An inventory of shedding data from clinical gene therapy trials

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Marjolein M. K. B. van Mierlo[1]
Gerard Wagemaker[2]
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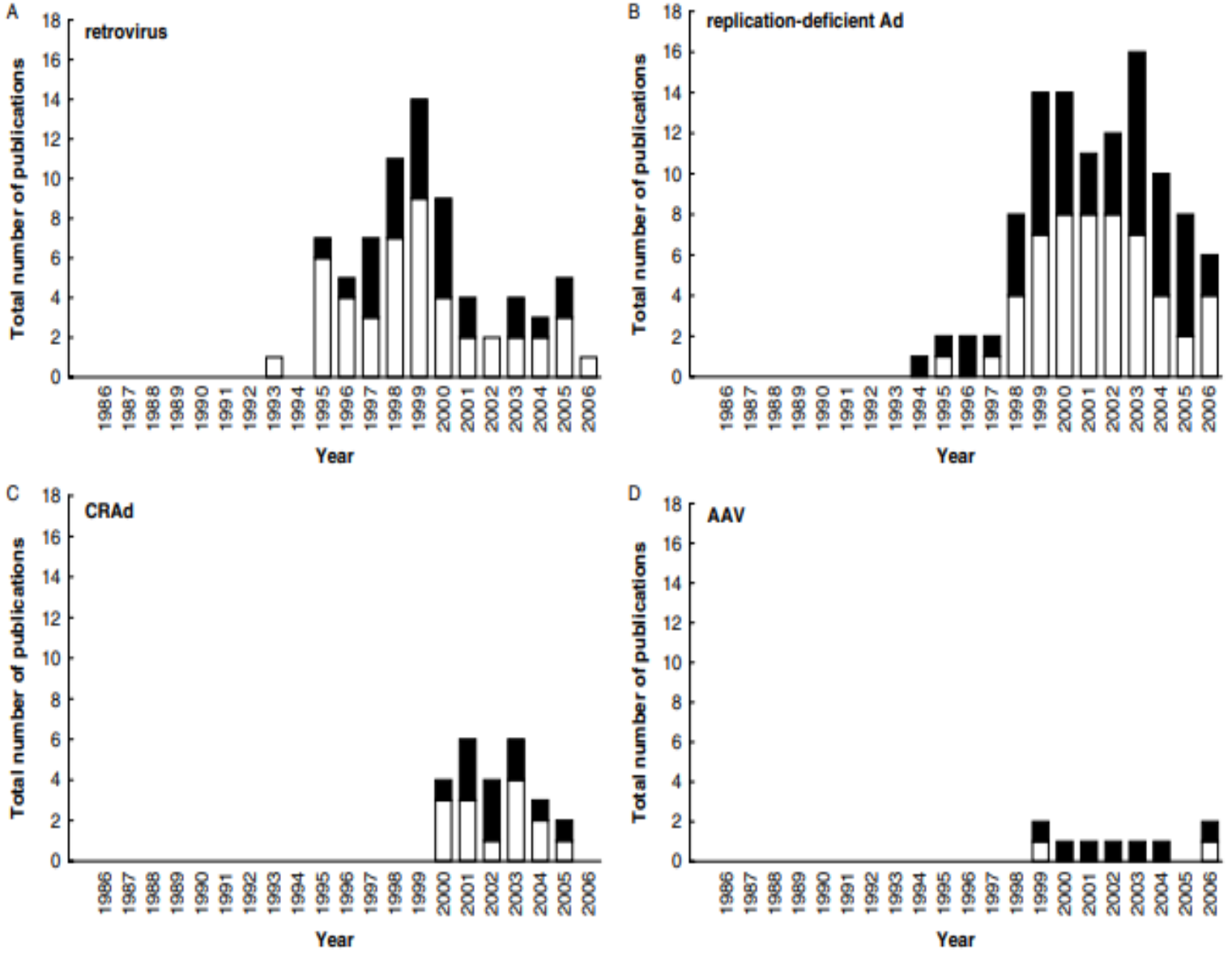
Abstract

Viruses are the most commonly used vectors for clinical gene therapy. The risk of dissemination of a viral vector into the environment via excreta from the treated patient, a phenomenon called shedding, is a major safety concern for the environment. Despite the significant number of clinical gene therapy trials that have been conducted worldwide, there is currently no overview of actual shedding data available. In this article, an inventory of shedding data obtained from a total of 100 publications on clinical gene therapy trials using retroviral, adenoviral, adeno-associated viral and pox viral vectors is presented. In addition, the experimental set-up for shedding analysis including the assays used and biological materials tested is summarized. The collected data based on the analysis of 1619 patients in total demonstrate that shedding of these vectors occurs in practice, mainly determined by the type of vector and the route of vector administration. Due to the use of non-quantitative assays, the lack of information on assay sensitivity in most publications, and the fact that assay sensitivity is expressed in various ways, general conclusions cannot be made as to the level of vector shedding. The evaluation of the potential impact and consequences of the observations is


A
retrovirus
B
replication-deficient Ad
C
CRAd
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AAV
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note that also in these cases blood can be a potential source for vector dissemination into the environment, although this is not regarded as shedding.

The effect of the administration route on vector shedding is most clear in two trials on AAV-mediated gene therapy for haemophilia B [90,91]. After intramuscular administration, shedding of the AAV vector was primarily observed during the first 2 days in saliva and serum and not in urine. The vector could not be detected in semen obtained after about 2 months [90]. In contrast, after infusion through the hepatic artery of the same vector, shedding was observed in urine during the first week. In addition, in 6 out of the 7 treated patients, vector DNA was found in semen up to 16 weeks after therapy [91]. Based on these observations, the FDA Biological Response Modifiers Advisory Committee (currently the Cellular, Tissue and Gene Therapies Advisory Committee) decided in 2002 that a positive semen test is no indication to put a clinical trial on hold, provided that the vector does not persist in semen longer than 1 year [100]. In that case, a trial will be halted in order to study the occurrence of germ-line transmission and to anticipate on the potential consequences of such an event. Furthermore, long-term monitoring of sperm was recommended by this committee.

Conclusions

Based on literature data on shedding of viral vectors during clinical gene therapy as presented in this overview, the following conclusions can be made:

- shedding of viral vectors occurs in practice;
- the majority of publications on clinical gene therapy trials do not report on shedding analysis;
- the occurrence of shedding mainly depends on the type of vector and the route of administration; and