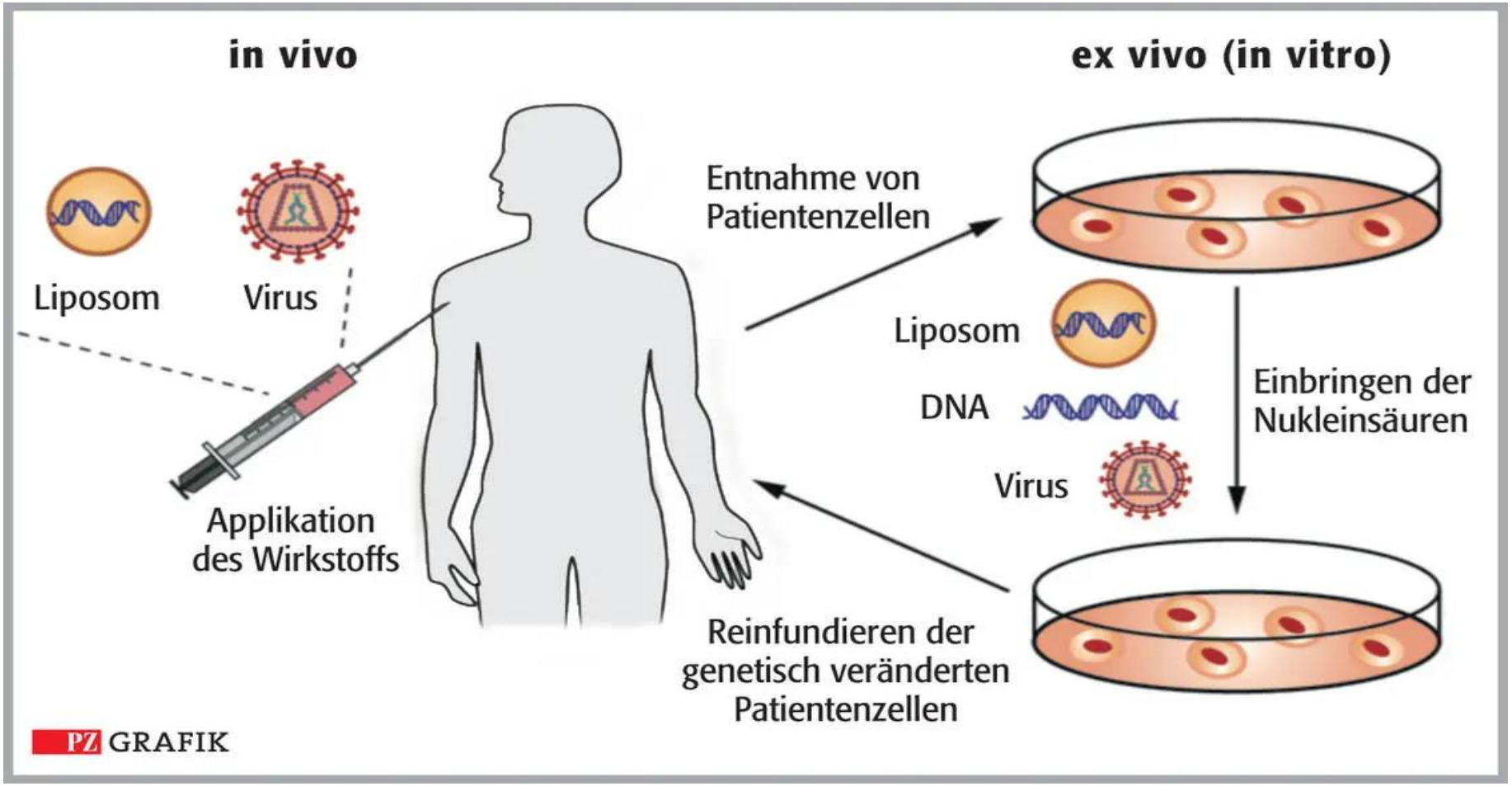
Gentherapie nov 2022



EU wet voor geneesmiddelen mens en dier 2001/83 – 2019/5(6)

Article 121a

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The power to adopt delegated acts referred to in Article 14(1), Article 22b, Article 23b, Article 46a, Article 47, Article 52b, Article 54a and Article 120 shall be conferred on the Commission for a period of five years from 26 July 2019. The Commission shall draw up a report in respect of the delegation of power not later than nine months before the end of the five-year period. The delegation of power shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

3. The delegation of power referred to in Article 14(1), Article 22b, Article 23b, Article 46a, Article 47, Article 52b, Article 54a and Article 120 may be revoked at any time by the European Parliament or by the Council. A decision to revoke shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

4. Before adopting a delegated act, the Commission shall consult experts designated by each Member State in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making ([15]).

5. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

6. A delegated act adopted pursuant to Article 14(1), Article 22b, Article 23b, Article 46a, Article 47, Article 52b, Article 54a and Article 120 shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or of the Council.

▼B▼

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02001L0083-20190726#M14-4

2001/83 – 2009/120

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.

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.

▼M6 ▼

4a. *Advanced therapy medicinal product* : A product as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products ([20]).

Centrale procedure
EU 2004/726 – 2019/5

Article 14-a

1. In duly justified cases, to meet unmet medical needs of patients, a marketing authorisation may, for medicinal products intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, be granted prior to the submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. In emergency situations, a marketing authorisation for such medicinal products may be granted also where comprehensive pre-clinical or pharmaceutical data have not been supplied.

2. For the purposes of this Article, 'unmet medical needs' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.

3. Marketing authorisations may be granted pursuant to this Article only if the risk-benefit balance of the medicinal product is favourable and the applicant is likely to be able to provide comprehensive data.

4. Marketing authorisations granted pursuant to this Article shall be subject to specific obligations. Those specific obligations and, where appropriate, the time limit for compliance shall be specified in the conditions to the marketing authorisation. Those specific obligations shall be reviewed annually by the Agency.

5. As part of the specific obligations referred to in paragraph 4, the holder of a marketing authorisation granted pursuant to this Article shall be required to complete ongoing studies, or to conduct new studies, with a view to confirming that the risk-benefit balance is favourable.

6. The summary of product characteristics and the package leaflet shall clearly mention that the marketing authorisation for the medicinal product has been granted subject to specific obligations as referred to in paragraph 4.

7. By way of derogation from Article 14(1), a marketing authorisation granted pursuant to this Article shall be valid for one year, on a renewable basis.

8. When the specific obligations referred to in paragraph 4 of this Article have been fulfilled, the Commission may, following an application by the marketing authorisation holder, and after receiving a favourable opinion from the Agency, grant a marketing authorisation valid for five years and renewable pursuant to Article 14(2) and (3).

9. The Commission is empowered to adopt delegated acts in accordance with Article 87b in order to supplement this Regulation by specifying:

(a) the categories of medicinal products to which paragraph 1 of this Article applies; and

(b) the procedures and requirements for granting a marketing authorisation pursuant to this Article and for its renewal.

▼M5 ↓

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004R0726-20190128#M7-29

Article 16a

1. Variations shall be classified in different categories depending on the level of risk to public health and the potential impact on the quality, safety and efficacy of the medicinal product concerned. Those categories shall range from changes to the terms of the marketing authorisation that have the highest potential impact on the quality, safety or efficacy of the medicinal product, to changes that have no or minimal impact thereon.

2. The procedures for examination of applications for variations shall be proportionate to the risk and impact involved. Those procedures shall range from procedures that allow implementation only after approval based on a complete scientific assessment to procedures that allow immediate implementation and subsequent notification by the marketing authorisation holder to the Agency.

3. The Commission is empowered to adopt delegated acts in accordance with Article 87b in order to supplement this Regulation by:

(a) specifying the categories in which variations shall be classified; and

(b) establishing procedures for the examination of applications for variations to the terms of marketing authorisations.

Variations 2008/1234 – 2121/756

▼A1

Article 21

Pandemic situation with respect to human influenza and human coronavirus

(1) By way of derogation from Chapters I, II, IIa and III, where a pandemic situation with respect to human influenza or human coronavirus is duly recognised by the World Health Organization or by the Union in the framework of Decision No 1082/2013/EU of the European Parliament and of the Council ([2]), the relevant authorities, or in the case of centralised marketing authorisations, the Commission may, where certain pharmaceutical, non-clinical or clinical data are missing, exceptionally and temporarily accept a variation to the terms of a marketing authorisation for a human influenza vaccine or a human coronavirus vaccine.

(2) The relevant authority may request the applicant to provide supplementary information in order to complete its assessment within a time limit set by it.

(3) Variations may be accepted pursuant to paragraph 1 only if the benefit-risk balance of the medicinal product is favourable.

(4) Where a variation is accepted pursuant to paragraph 1, the holder shall submit the missing pharmaceutical, non-clinical and clinical data within a time limit set by the relevant authority.

(5) In the case of centralised marketing authorisations, the missing data and the time limit for submission or compliance shall be specified in the conditions to the marketing authorisation. Where the marketing authorisation has been granted in accordance with Article 14-a of Regulation (EC) No 726/2004 this may be done as part of the specific obligations referred to in paragraph 4 of that Article.

▼B▲

Article 22

Urgent safety restrictions

▼M1▲

1. Where, in the event of a risk to public health in the case of medicinal products for human use or, in the case of veterinary medicinal products, in the event of a risk to human or animal health or to the environment, the holder takes urgent safety restrictions on its own initiative, it shall forthwith inform all relevant authorities and, in the case of a centralised marketing authorisation, the Agency.

If the relevant authority or, in the case of a centralised marketing authorisation, the Agency has not raised objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed accepted.

▼B▲

2. In the event of a risk to public health in the case of medicinal products for human use or, in the case of veterinary medicinal products, in the event of a risk to human or animal health or to the environment, relevant authorities or, in the case of centralised marketing authorisations, the Commission may impose urgent safety restrictions on the holder.

3. Where an urgent safety restriction is taken by the holder or imposed by a relevant authority or the Commission, the holder shall submit the corresponding application for variation within 15 days following the initiation of that restriction.

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1234-20210513#M2-2

SECTION 2

Amendments to the decision granting the marketing authorisation and implementation

Article 23

Amendments to the decision granting the marketing authorisation

▼M1 ↓

1. Amendments to the decision granting the marketing authorisation resulting from the procedures laid down in Chapters II and IIa shall be made:

(a) in the case of major variations of type II, within two months following receipt of the information referred to in Article 11(1)(c) and Article 13e(a), provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned;

(b) in the other cases, within six months following receipt of the information referred to in Article 11(1)(c) and Article 13e(a), provided that the documents necessary for the amendment of the marketing authorisation have been transmi tted to the Member States concerned.

▼M1 ↓

1a. Amendments to the decision granting the marketing authorisation resulting from the procedures laid down in Chapter III shall be made:

(a) within two months following receipt of the information referred to in Article 17(1)(c) for the following variations:

(i) variations related to the addition of a new therapeutic indication or to the modification of an existing one;

(ii) variations related to the addition of a new contraindication;

(iii) variations related to a change in posology;

(iv) variations related to the addition of a non-food producing target species or the modification of an existing one for veterinary medicinal products;

(v) variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine;

(vi) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

(vii) variations related to changes to the withdrawal period for a veterinary medicinal product;

(viii) other type II variations that are intended to implement changes to the decision granting the marketing authorisation due to a significant public health concern or significant animal health or environmental concern in the case of veterinary medicinal products;

▼M2 ↓

(ix) variations related to changes to the active substance of a human coronavirus vaccine, including replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences;

ANNEX I

Extensions of marketing authorisations

1. Changes to the active substance(s):

(a) replacement of a chemical active substance by a different salt/ester complex/derivative, with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different;

(b) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different;

▼M2 ↓

(c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy and/or safety characteristics are not significantly different, with the exception of:

— changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

— replacement or addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine;

— replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;

— replacement of a strain for a veterinary vaccine against equine influenza;

▼B ↓

(d) modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different;

(e) a new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy/safety characteristics are not significantly different;

https://www.ema.europa.eu/en/documents/agenda/agenda-cat-agenda-14-16-july-2021-meeti

Onderwerp: [redacted] gemandateerde Collegevergadering van 11 augustus geannuleerd
Datum: donderdag 29 juli 2021 14:33:20
Bijlagen: image001.png
image002.gif

Geachte Collegeleden,
Omdat voor de gemandateerde **Collegevergadering van 11 augustus** slechts één agendapunt is aangeleverd, is besloten om deze **vergadering te annuleren**.
Het openstaande agendapunt ([redacted]) betreft een [redacted]

- [redacted]
- [redacted]

Met vriendelijke groet,
[redacted]
[redacted] College ter Beoordeling van Geneesmiddelen
CBG MEB - logo NL - RGB e-mail

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

https://www.ema.europa.eu/en/documents/minutes/minutes-cat-meeting-8-10-december-20

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).

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2015
EMA/CAT/600280/2010 rev.1
Committee for Advanced Therapies (CAT)

Reflection paper on classification of advanced therapy medicinal products

Draft Agreed by CAT	June 2014
Adoption by CAT for release for consultation	20 June 2014
Start of public consultation	30 June 2014
End of consultation (deadline for comments)	31 October 2014
Draft Agreed by CAT	13 May 2015
Adoption by CAT	22 May 2015

Keywords	***ATMP classification, Gene therapy, Somatic cell therapy, Tissue engineered Products, Combined ATMPs***

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

2.3.3. Gene therapy medicinal product versus cell therapy medicinal product

Another borderline scenario relates to products that are modified by adding a mRNA sequence, for example dendritic cells (DC) electroporated with mRNA in vitro and administrated to the patient to elicit a specific immune response. One could argue that the claimed mechanism of action is directly related to the expression of the mRNA encoded antigens to stimulate e.g. tumour specific immune responses. However, due to its relatively short half-life there may be little or no residual mRNA at the time of re-administration of the dendritic cells to the patient. Thus, it can be claimed that a recombinant nucleic acid is not administered to human beings with a view to adding a genetic sequence, but rather the mRNA electroporated DCs could be seen as an intermediate in the manufacturing process where the phenotype is finally altered without alteration of the genotype of the cells. Therefore, the product was considered not to comply with the definition of a gene therapy medicinal product. Instead the CAT considered that the product was a somatic cell therapy product as it consists of cells which were administered to human beings with a view to treating a disease through the immunological action of the modified cell populations.

International Commission for Harmonisation

Progress on existing ICH Guidelines

ICH's Working Groups have also continued to progress their virtually. The Assembly was updated on the status of ICH's current thirty-four Working Groups, and the dedicated efforts of ICH experts to progress their harmonisation activities in the face of pandemic related challenges. The Assembly noted significant milestones reached by several Working Groups including:

- Step 3 Working Group consensus and Step 4 Regulatory Member endorsement reached for the Q3C(R8) Guideline on Impurities: Guideline for Residual Solvents, revised to include the Permitted Daily Exposure (PDE) levels for 2-Methyltetrahydrofuran, Cyclopentyl Methyl Ether and Tertiary Butyl Alcohol.
- Step 3 Working Group consensus and Step 4 Regulatory Member endorsement reached for the M8 eCTD v4.0 Question and Answer (Q&A) Document v.1.5, Specification for Submission Format for eCTD v.1.3, and eCTD v4.0 Implementation Package v.1.4.
- Step 1 Working Group consensus and Step 2 Assembly and Regulatory Member endorsement reached for the draft ICH S1B(R1) Addendum to the Guideline on Testing for Carcinogenicity of Pharmaceuticals.
- Step 1 Working Group consensus and Step 2 Assembly and Regulatory Member endorsement reached for the new, draft ICH S12 Guideline on Nonclinical Biodistribution Considerations for Gene Therapy Products.

The Assembly additionally noted significant progress made on the revision of the ICH E6 Guideline on Good Clinical Practice with the recent publication of a draft principles document, which were subsequently presented at two global public web conferences in May 2021. ICH hopes that sharing the draft version of the principles will facilitate transparency and better understanding on the revision of this important guideline which is widely used by clinical trial researchers and has significant impact for trial participants and patients.

ICH
harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2021
EMA/CHMP/ICH/318372/2021
Committee for Medicinal Products for Human Use

ICH guideline S12 on nonclinical biodistribution considerations for gene therapy products

Step 2b

Transmission to CHMP	24 June 2021
Adoption by CHMP	24 June 2021
Release for public consultation	24 June 2021
Deadline for comments	24 October 2021

Comments should be provided using this template. The completed comments form should be sent to ich@ema.europa.eu

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ich-guideli

1.3. Scope

GT products within the scope of this guideline include products that mediate their effect by the expression (transcription or translation) of transferred genetic materials. Some examples of GT products can include purified nucleic acid (e.g., plasmids and RNA), microorganisms (e.g., viruses, bacteria, fungi) genetically modified to express transgenes (including products that edit the host genome), and *ex vivo* genetically modified human cells. Products that are intended to alter the host cell genome *in vivo* without specific transcription or translation (i.e., delivery of a nuclease and guide RNA by non-viral methods) are also covered in this guidance. Although not currently considered GT in certain regions, the principles outlined in this guideline are also applicable to oncolytic viruses that are not genetically modified to express a transgene. This guideline does not apply to prophylactic vaccines. Chemically synthesised oligonucleotides or their analogues, which are not produced using a biotechnology-based manufacturing process, are outside the scope of this guideline. The release of a GT product outside the body via excreta (feces), secreta (urine, saliva, nasopharyngeal fluids, etc.), or through the skin (pustules, sores, wounds) is termed 'shedding'. Evaluation of the nonclinical shedding profile of a GT product is outside the scope of this guideline. Assessment of genomic integration and germline integration of GT products are also outside the scope of this guideline.

5. SPECIFIC CONSIDERATIONS

5.1. Assay Methodologies

Evaluation of the BD profile necessitates quantitating the amount of genetic material (DNA/RNA) of the GT product in tissues/biofluids and, if appropriate, expression products. Currently, real-time quantitative polymerase chain reaction (qPCR) is considered the 'gold standard' for measurement of specific DNA (or, with a reverse transcription step, RNA as well) presence in tissues/biofluids. Quantification of nucleic acid sequences is important for assessing the relative amount of genetic material from a GT product and determining the kinetics of its accumulation or decay. The limit of sensitivity and reproducibility of the quantification method should be established and documented. Spike and recovery experiments, considered part of assay development, should be performed to demonstrate the ability to detect the target sequence in different tissues/biofluids. Other techniques can be used in nonclinical studies to monitor BD of a vector and/or the expression products. These include, but are not limited to: enzyme-linked immunosorbent assay (ELISA); immunohistochemistry (IHC); western blot; *in situ* hybridisation (ISH); digital PCR; flow cytometry; various *in vivo* and *ex vivo* imaging techniques; and other evolving technologies. It is important to provide a comprehensive description of the methodology and the justification for the technique used, including the performance parameters of the method.

6. APPLICATION OF NONCLINICAL BD STUDIES

Characterisation of the BD profile following administration of a GT product in animals is a critical component of a nonclinical development programme. The nonclinical BD data contribute to the overall interpretation of the study findings to enable a better understanding of the relationship of various findings (desired and undesired) to the administered GT product. Attribution of findings observed in the dosed animals to the genetic material (DNA/RNA) and/or to the expression product factor into ascertaining a potential benefit: risk profile of the GT product before administration in humans. It is important to consider the relevancy of the BD data to the clinical population based on factors such as the ROA, dose level(s), dosing regimen, and animal immune response. These data can also inform elements of a first-in-human trial and subsequent clinical trials, such as the dosing procedure (i.e., dosing intervals between subjects), the monitoring plan, and long-term follow-up assessment.

NOTES

1. In general, it is recommended that a minimum of 5 rodents or 3 non-rodents per sex/group/time point be evaluated; however, inclusion of equivalent numbers for each sex may not be critical. Justification for these decisions should be provided.
2. For each delivery device system used, it is important to provide data that verify the volume and dose level of the administered GT product in animals. This information can affect interpretation of the resulting BD profile. If a novel delivery device system is planned for use in clinical trials, consider collecting BD data in conjunction with the pharmacology and/or toxicology studies conducted with the device system or its equivalent.

	Comment and rationale	Proposed changes / recomm
	Regarding guide RNA manufactured using either chemical or in vitro transcription, there is a difference between the US and Europe about this. But generally, whether or not oligonucleotides are chemically synthesized should not matter when used as gRNA for in vivo or ex vivo gene editing.	
	In this case, inclusion of oncolytic viruses in these guidelines (labeled gene therapy products) seems incorrect.	
	It is currently stated that prophylactic vaccines are outside of scope. Although prophylactic vaccines are excluded from the EMA definition of ATMP, they should not be excluded from this guidance since the same development principles apply to a given GT product modality (e.g. mRNA) whether it is intended to be used as a preventative vaccine against infectious disease or as a cancer treatment.	Remove "prophylactic vaccine"

https://www.ema.europa.eu/en/documents/comments/overview-comments-received-ich-g

	Please place this definition above "Expression products" and add to the "Gene Therapy Products" definition the following text at the end - "For the definition of the mRNA or protein that results from transcription and/or translation of the nucleic acid within the gene therapy product, see definition of 'Expression product'".

	Chemically synthesized guide RNA should be within scope not outside of scope when used for gene editing.
	Guideline Language: Chemically synthesised oligonucleotides or their analogues, which are not produced using a biotechnology-based manufacturing process, are outside the scope of this guideline. Comment: There are circumstances where a chemically synthesized (i.e., an LNP incapsulated) could be delivered and qualified as a gene therapy. Why are these not in scope?
	Shedding samples are often collected in the same studies as BD/safety and utilize the same methodology. The IPRP reflection paper stated "Shedding studies and germline transmission studies for gene therapy products are outside the scope"
	Could a reference to the shedding guidelines be included?
	Viral shedding is listed as "out of scope". We believe that it is a missed opportunity in not including this topic, particularly as some would consider shedding as part of the "distribution" of a gene therapy vector. In addition, there exists significant health authority divergence in opinion with respect to whether shedding should be assessed in nonclinical studies. Please consider adding shedding within this guidance. Other suggestion could be to ask updating the ICH shedding guideline and refer to it.

Comment: The section is clear that biodistribution should be evaluated prior to clinical studies. Would it be worth including a statement that specifies if the vector system is novel / uncharacterised? If a sponsor is using a well characterised vector that has been explored previously in BD studies perhaps this can be omitted from the non-clinical package. For example if a platform technology just switched a transgene that is in the same vector with an identical promotor / expression system.

If possible, define persistence (e.g., detectable vector, gene product beyond 3 months in a rodent or 6 months in a non-human primate). Alternately, does the ability to demonstrate large decreases in analytes within gonads over time suffice to suggest lack or waning persistence? The latter scenario seems to be a fairly common outcome, and is consistent with
the ICH Considerations documents which says: "If the vector is present in the gonads, animals should be studied to assess whether the level of vector sequence falls below the assay's limit of detection at later time points (i.e., transient detection)."

Despite it stated that assessment of genomic and germline integration being outside of this guideline, it might be helpful to contain a clearer recommendation with regard to "integration potential" in this guidance document, if such integration analyses of gonadal tissue is recommended (or required per region) (in addition to determination of vector copy number) and if a single rodent species is sufficient.
[Presumably integration profile does not refer to an in situ homology search to the delivered nucleic acid].

In light of higher than previously thought integration frequency of AAV vectors, sponsors may not have a clear understanding of what ICH are advising with regard to possible ITR-transgene-ITR integrants that could possibly be detected in germline or germline cells.

Further to reference to ICH Considerations: General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors, Oct 2006.294, it could be considered helpful to refer to EMEA.273974.2005. Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors, which goes further than the ICH consideration with regard to stating how no gene therapy trials may be carried out which result in modifications to the subjects' s germline genetic identity (Cf. Directive 2001/20/EC).

1.2. Adoption of agenda

The CAT agenda for 07-09 September 2022 meeting was adopted with two additions:

- Strategic Review and Learning meeting under the Swedish Presidency of the European Union;

- EMA Regulatory & scientific conference on RNA based medicines.

https://www.ema.europa.eu/en/documents/minutes/minutes-cat-meeting-7-9-september-2022_

https://www.ema.europa.eu/en/documents/agenda/agenda-prac-meeting-5-7-october-20

7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

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

Rapporteur: Martijn van der Plas

Action: For adoption

7.4. Cooperation with the EU regulatory network

7.4.1. Regulatory & scientific conference on RNA-based medicines

Scope: Draft agenda of the conference that is scheduled to take place on 2 February 2023.

Action: for discussion

AskEMA - Response to ASK-121831 - new active substance

Inbox ×

AskEMA No-Reply <AskEMA.noreply@ema.europa.eu> Thu, Sep 29, 12:39 PM

to me

Dear Drs Engels
Many thanks for your question.
The reflection paper on New Active Substance criteria for biological medicinal product (including advanced therapy medicinal products) has not yet been published.
The finalisation of this paper has taken much more time, as it involved extended consultations with all internal stakeholders.
We expect that this paper will be published on the EMA website, for public consultation, by the end of October 2022.
I hope this information is helpful.
Best regards
Patrick Celis
ATMP Office

Vaccine	Marketing authorisation holder	Key milestones
Comirnaty(developed by BioNTech and Pfizer)	BioNTech Manufacturing GmbH	Conditional marketing authorisation issued: 21/12/2020 Annual renewal issued: 03/11/2021 Standard marketing authorisation issued: 10/10/2022
COVID-19 Vaccine (inactivated, adjuvanted) Valneva	Valneva Austria GmbH	Marketing authorisation issued: 24/06/2022
Spikevax (previously COVID-19 Vaccine Moderna)	Moderna Biotech Spain S.L.	Conditional marketing authorisation issued: 06/01/2021 Annual renewal issued: 04/10/2021 Standard marketing authorisation issued: 03/10/2022
Vaxzevria (previously COVID-19 Vaccine AstraZeneca)	AstraZeneca AB	Conditional marketing authorisation issued: 29/01/2021 Annual renewal issued: 09/11/2021 Standard marketing authorisation issued: 31/10/2022
VidPrevtyn Beta	Sanofi Pasteur	Marketing authorisation 10/11/2022

Comirnaty

Share RSS

tozinameran / riltozinameran and tozinameran / famtozinameran and tozinameran / COVID-19 mRNA Vaccine (nucleoside modified)

AUTHORISED
This medicine is authorised for use in the European Union.

PATIENT SAFETY
Patient safety information

Table of contents

Overview

Comirnaty is a vaccine for preventing coronavirus disease 2019 (COVID-19) in people from the age of 6 months.

Comirnaty contains tozinameran, a messenger RNA (mRNA) molecule with instructions for producing a protein from the original strain of SARS-CoV-2, the virus that causes COVID-19.

Comirnaty is also available as two adapted vaccines:

- Comirnaty Original/Omicron BA.1 contains tozinameran and riltozinameran, another mRNA molecule with instructions for producing a protein from the Omicron BA.1 subvariant of SARS-CoV-2.
- Comirnaty Original/Omicron BA.4-5 contains tozinameran and famtozinameran, another mRNA molecule with instructions for producing a protein from the Omicron BA.4 and BA.5 subvariants of SARS-CoV-2.

The adapted vaccines are only used in people aged 12 years and older who have received at least a primary vaccination course against COVID-19.

Comirnaty and its adapted vaccines do not contain the virus itself and cannot cause COVID-19.

Expand section Collapse section

Adapted vaccines are intended to provide broader protection against different virus variants following initial vaccination.

Companies need to submit an application to change the marketing authorisation of the originally authorised vaccine.

The table lists adapted vaccines that are already authorised or under evaluation.

Show 25 entries Search:

Vaccine	Marketing authorisation holder	Key milestones	More information
Comirnaty (developed by BioNTech and Pfizer)	BioNTech Manufacturing GmbH	**Comirnaty Original/Omicron BA.1** Authorisation issued: 01/09/2022 **Comirnaty Original/Omicron BA.4-5** Authorisation issued: 12/09/2022	Latest news
Spikevax (previously COVID-19 Vaccine Moderna)	Moderna Biotech Spain S.L.	**Spikevax bivalent Original/Omicron BA.1** Authorisation issued: 01/09/2022 **Spikevax bivalent Original/Omicron BA.4-5** Authorisation issued: 20/10/2022	Latest news

EC approves Sanofi, GSK's VidPrevtyn Beta Covid-19 booster vaccine

By NS Healthcare Staff Writer 11 Nov 2022

PHARMACEUTICALS REGULATION

VidPrevtyn Beta is a monovalent, recombinant-protein, next-generation Covid-19 vaccine developed by Sanofi, leveraging GSK's pandemic adjuvant, and is modelled based on the Beta variant of SARS-CoV-2

pharmacovigilance activities: Myocarditis and Pericarditis

Myocarditis and Pericarditis	
Evidence for linking the risk to the medicine	Myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines, mainly in males under the age of 40 years within 14 days after a second dose. However, cases have also been reported in older males, in females, and following other doses. There are limited data on the risk of myocarditis following third and subsequent booster doses. However, the risk after the third dose seems to be lower than following the second dose. [a] The observed risk is highest in males 12 to 17 years of age. While some cases required intensive care support, available data from short-term follow-up suggest that symptoms resolve in most individuals with conservative management. Information is not yet available about potential long-term sequelae. [b, c] The risk of myocarditis is greater after SARS-CoV-2 infection than after COVID-19 vaccination and remains modest after sequential doses including a booster dose of Pfizer BioNTech mRNA vaccine. An increased risk of myocarditis is observed at 1-7 days (IRR 21.08, 95% CI 15.34, 28.96), 8-14 days (IRR 11.29, 95% CI 7.70, 16.57), 15-21 days (IRR 5.36, 95% CI 3.24, 8.89) and 21-28 days (IRR 3.08, 95% CI 1.65, 5.75) following a positive test. [d] Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of Novavax COVID-19 vaccine, which is manufactured using a protein/adjuvant platform and a different adjuvant system than the CoV2 preS dTM vaccine. [e] Considering limited safety data, the available evidence is not yet fully sufficient to rule out myocarditis and pericarditis as a safety concern. Thus, it is added as an important potential risk.
Risk factors and risk groups	Adolescent and young adult males following the second dose of vaccine may be at higher risk. [f, g]
Risk minimization measures	**Routine risk minimization measures:** None **Additional risk minimization measures:** None

AS03

From Wikipedia, the free encyclopedia

AS03 (for "Adjuvant System 03") is the trade name for a squalene-based immunologic adjuvant used in various vaccine products by GlaxoSmithKline (GSK). It is used, for example, in GSK's A/H1N1 pandemic flu vaccine Pandemrix. It is also in Arepanrix and the Q-pan for H5N1 influenza.[1]

A dose of AS03 adjuvant contains[2]

- 10.69 mg squalene
- 11.86 mg DL-α-tocopherol
- 4.86 mg polysorbate 80

In the 2009 influenza pandemic, vaccines containing AS03 delivered a stronger immunogene response against pandemic H1N1 influenza than non-adjuvanted vaccines, despite their containing lower levels of viral antigen.[3]

Small observational studies reported from Finland and Sweden in 2012, and larger studies from Ireland reported in 2012, and reported in each of England, Norway and France in 2013, found an association between narcolepsy and an A(H1N1)pdm09 vaccine that used AS03 adjuvant; the rates ranged from one in 16,000 doses to one in 50,000 doses.[4] As of 2016 it was unclear whether or not the adjuvant was responsible; other suspected causes include genetic susceptibility, exposure to A(H1N1)pdm09, manufacturing impurities, and combinations of these factors.[4]

References [edit]

1. ^ "FDA panel endorses H5N1 vaccine with adjuvant". 15 Nov 2012.
2. ^ Pandemrix – Summary of product characteristics Archived October 7, 2009, at the Wayback Machine, European Medicines Agency websiteEuropean Medicines Agency website Archived 2013-07-15 at the Wayback Machine
3. ^ Yin JK, Khandaker G, Rashid H, Heron L, Ridda I, Booy R (September 2011). "Immunogenicity and safety of pandemic influenza A (H1N1) 2009 vaccine: systematic review and meta-analysis". *Influenza and Other Respiratory Viruses*. **5** (5): 299–305. doi:10.1111/j.1750-2659.2011.00229.x. PMC 4986623. PMID 21668694.
4. ^ [a] [b] Ahmed, SS; Montomoli, E; Pasini, FL; Steinman, L (2016). "The Safety of Adjuvanted Vaccines Revisited: Vaccine-Induced Narcolepsy" (PDF). *The Israel Medical Association Journal*. **18** (3–4): 216–20. PMID 27228647.

"Though research remains ongoing, currently available scientific data suggests that the occurrence of narcolepsy in the context of the 2009/10 Flu pandemic was associated with a similarity between a protein in the wild type H1N1 virus and a human protein relevant in regulating the sleep cycle, an extremely rare coincidence. Because the similarity was specific to the wild type H1N1 Flu virus, it is unlikely to affect the potential development and use of future 2019-nCOV pandemic vaccine candidates," a spokesperson for GSK said in an emailed statement.

Editor's note: This article was updated with a statement from GSK.

https://www.fiercebiotech.com/biotech/gsk-makes-adjuvant-available-to-coronavirus-vac

About BARDA support

Research and development for the vaccine are supported by U.S. federal funds from the Biomedical Advanced Research and Development Authority (BARDA), part of the office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services in collaboration with the U.S. Department of Defense Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense under Contract # W15QKN-16-9-1002 and the National Institute of Allergy and Infectious Diseases (NIAID).

About the Sanofi and GSK partnership

In the collaboration between the two companies, Sanofi provides its recombinant antigen and will be the marketing authorisation holder. GSK contributes with its pandemic adjuvant, both established vaccine platforms that have proven successful against influenza.