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

The rapporteur presented the final version of the NAS reflection paper.

CAT adopted the reflection paper for a 6-month public consultation.

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

The draft agenda was presented. The meeting will be chaired by Sol Ruiz and EMA's chief medical officer . CAT members were asked to provide suggestions of academic speakers to be invited to this conference.

7.4.2. Revision of the EU legislation on blood, tissues and cells (BTC)

CAT: Ilona Reischl

Scope: Analysis of the BTC proposal by a CAT member

https://www.ema.europa.eu/en/committees/cat/cat-agendas-minutes-reports

2.1. Definition of Active Substance

According to Article 1(3a) of Directive 2001/83/EC, active substance is defined as "any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis".

The Directive further defines in Annex I, Part I, Section 3.2.1 "biological [active] substance" as a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control (see Glossary for further details).

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-criteria-be-considered-evaluation-new-active-substance-nas-status-biological_en.pdf

4. Would a vaccine antigen produced from a new viral or bacterial strain be considered to be a new active biological substance?

Yes, a vaccine antigen produced from a new viral or bacterial strain would likely be considered to be a new active substance. This is without prejudice to Articles 12, 13f, 18 and 21 of Regulation (EC) No 1234/2008.

5. Would a second conjugated versus an authorised conjugated vaccine antigen be considered to be a new active biological substance when using a different carrier molecule?

Yes. Due to the difference in carrier structure (which has a immunological action in itself), the second conjugated vaccine would likely be considered NAS (first indent NtA definition).

Example:

If an antigen was to be prepared by conjugation with CRM_{197} and the authorised antigen was conjugated to a tetanus toxoid, the CRM conjugated antigen would likely to be considered a NAS.

7. Would the presence of a protein variant (due to misincorporation) in addition to the desired protein, could qualify as a NAS ?

No. It is acknowledged that due to misincorporation (especially under limited feeding conditions) variants may be present at levels of a few percent, where amino acids substituted. These would likely be qualified as product related substances in the total mixture which constitutes the active substance.

8. For biological active substances comprising mRNA, would a difference in the mRNA sequence (protein encoding or regulatory/untranslated) be considered a new active substance?

Yes, provided sufficient evidence is submitted that the differences in the mRNA sequence are substantial.

4.1.2. In vivo gene therapy

A first indent NAS claim could be justified by substantial differences in biological characteristics and/or biological activity and/or (to the extent that is technically possible to define basic structural features) in basic structural elements, of the active substance, including differences caused by the manufacturing technology. The following is a non-exhaustive list of examples:

i. *Differences in the transfer system*: A difference in the transfer system when being part of the active substance (e.g. viral vector system vs. non-viral vector system) is expected to be a substantial difference that could justify a first indent NAS claim.

ii. *Differences in the viral vector*: A difference in the viral vector (e.g. adenovirus vs. AAV) is expected to be a substantial difference that could justify a first indent NAS claim.

In addition, a difference in virus capsid due to the use of a different (sub-)type of virus vector or the presence of different capsid proteins is expected to be a substantial difference that could justify a first indent NAS claim.

The above examples are not exhaustive, other substantial differences in the viral sequence (e.g. differences that reduce the risk of insertional mutagenesis or the risk of formation of replication competent viruses, as well as differences associated with the integration profile) could also justify a first indent NAS claim.

iii. *Differences in the therapeutic sequence:* A difference in the therapeutic sequence resulting in a substantial difference in amino acid sequence of the therapeutic protein could justify a first indent NAS claim.

Regulatory and scientific virtual conference on RNA-based medicines

2 February 2023, 09:00 – 16:30 (CET)

Background and objectives

The European Medicines Agency (EMA) is convening a virtual conference on 2 February 2023 to promote the development of RNA-based medicines, with the following objectives:

- To identify scientific and regulatory opportunities and challenges of RNA-based innovative medicines;
- To facilitate dialogue between industry/academia and regulators and raise awareness on scientific and regulatory aspects of emerging RNA technologies;
- To identify gaps in regulatory science.

This initiative addresses Goal 1 (Catalysing the integration of science and technology in medicines development) of the EMA Regulatory Science Strategy to 2025.

The conference focuses on emerging RNA technologies beyond vaccines.

RNA technologies for gene editing and primary prevention of infectious diseases is not within the scope of this event.

Session 1: State of the art of RNA technologies

Moderated by Falk Ehmann (EMA)

09:45 – 10:30	**Emerging trends on RNA technologies and synthetic oligonucleotide** ***Regulators' perspective:*** *Sol Ruiz, Spanish Agency of Medicines and Medical Products (AEMPS), ES* ***Industry perspective:*** *Tal Zaks, OrbiMed, US* ***Academic perspective:*** *Annemieke Aartsma-Rus, Leiden University Medical Center, NL*	**45'**
10:30 – 10:45	**Q&A**	**15'**
10:45 – 11:00	**Coffee break**	**15'**

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

NONCLINICAL BIODISTRIBUTION CONSIDERATIONS FOR GENE THERAPY PRODUCTS
S12

Draft version

Endorsed on 3 June 2021

Currently under public consultation

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ich-guideline-s12-nonclinical-biodistribution-considerations-gene-therapy-products-step-2b_en.pdf

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.

EU-IN Secretariat
to EU-IN, me

Thu, Jan 26, 3:39 PM (5 days ago)

Dear Mr Engel,

Thank you very much for your email.

The conference will be broadcast live without registration required. The link to the broadcast will be published on the event page on the day of the conference.

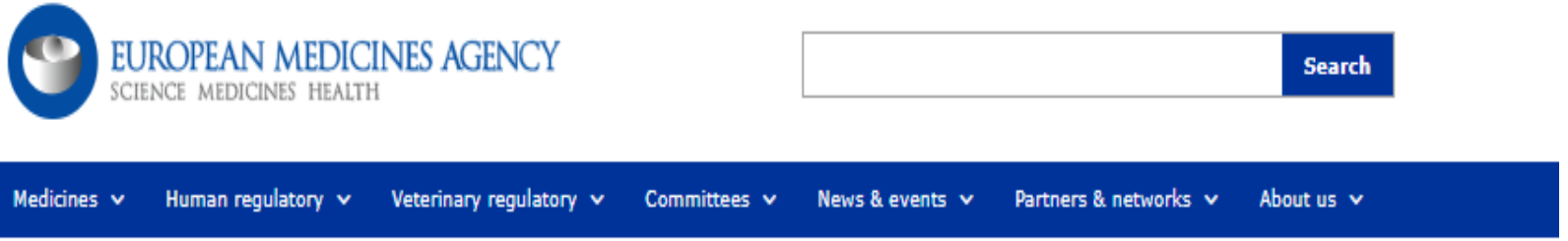
The conference will also be recorded and the recording will be available on the EMA website a few weeks after the event.

Please do not hesitate to contact me, should you require additional information.

With kind regards,

Aline

Aline Caromelle



Regulatory and scientific virtual conference on RNA-based medicines

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Date: 02/02/2023

Location: Online, 09:00 - 16:30 Amsterdam time (CET)

https://www.ema.europa.eu/en/events/regulatory-scientific-virtual-conference-rna-based-medicines