European Association of Hospital Pharmacists (EAHP) guidance on the pharmacy handling of *in vivo* gene therapy medicinal products

Joan Vinent Genestar[1], Sylvain Auvity[2], Nanna Christiansen[3], Heidi Ekelund[4], Liesbeth Huys[5], Helle Bach Ølgaard McNulty[6], Marcello Pani[7], Vera Pires[8], Bertrand Pourroy[9], Nicola Stoner[10]

[1]Hospital Sant Joan de Déu, Barcelona, Spain
[2]Necker Hospital, Assistance Publique-Hôpitaux de Paris, University of Paris, Paris, France
[3]Women's and Children's Services, Guy's and St Thomas' NHS Trust, London, UK
[4]ATMP Center, Sahlgrenska University Hospital, Gothenburg, Sweden
[5]Ghent University Hospital, Ghent, Belgium
[6]Capital Region Pharmacy, Herlev, Denmark
[7]Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[8]Portugese Institute of Oncology, Lisbon, Portugal
[9]ONCOPHARMA unit, La Timone University Teaching Hospital, Assistance Publique-Hopitaux, Marseille, France
[10]Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Supplementary appendices

Appendix 1. Glossary of Terms

Term	Definition
Accidental exposure	Accidental release of the GTMP from containment, resulting in unintended exposure of staff or the public to the agent.
Administration	The process of treating the patient with the GTMP that has been made ready-to-administer.
Advanced therapy medicinal product (ATMP)	A GTMP, somatic cell therapy medicinal product, or a tissue engineered product (1).
Biosafety	The safe working practices required for the handling of biological materials, especially infectious agents.
Biosafety level 1	The containment level required for a microorganism that is unlikely to cause human or animal disease (no or low individual and community risk; risk group 1). Often no biosafety device is required for this level; check local regulations (2).
Biosafety level 2	The containment level required for a pathogen that can cause human or animal disease, but is unlikely to be a serious hazard. Laboratory exposure could cause serious infection, but effective treatment and prevention measures are available and the risk of spread is limited (moderate individual risk, low community risk; risk group 2). Biosafety device, PPE and biohazard sign usually required; check local regulations (2).
Biosafety level 3	The containment level required for a pathogen that causes serious human or animal disease but does not usually spread between individuals. Effective treatment and preventative measures are available (high individual risk, low community risk; risk group 3). Biosafety device, PPE, biohazard sign, controlled access and directional airflow usually required; check local regulations (2).
Biosafety level 4	The containment level required for a pathogen that usually causes serious human or animal disease and is easily transmissible. Effective treatment and preventative measures are not usually available (high individual and community risk; risk group 4). Highly restricted access with airlock entry, shower exit and specialist waste disposal usually required. Specialised PPE and/or class 3 biosafety devices may be required, as well as additional safety measures; check local requirements (2).
Containment	The culturing, storage, transport, destruction, disposal, or any other use of a genetically modified organism within the bounds of physical, chemical and/or biological barriers to limit their contact with people and the environment (3) .
Decontamination	Any process for removing/killing microorganisms (2).
Disinfection	A physical or chemical means of killing microorganisms, but not necessarily spores (2).
Genetically modified organism (GMO)	An organism that has undergone genetic modification.
Genetic modification	Occurs when the genetic material of an organism has been altered in a way that does not occur naturally (either by mating or natural recombination), and uses recombinant nucleic acid techniques to form new combinations of genetic material (3).

Gene therapy	Treatment or prophylaxis of disease by the deliberate introduction of genetic material into the isolated cells of a patient (*ex vivo*) or directly into the patient (*in vivo*) (4).
Gene therapy medicinal product (GTMP)	A GTMP must fulfil two conditions: 1) the product must be a biological medicinal product and contain 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 (1).
Handling	Includes storage, dispensing and reconstitution, transportation, administration, waste disposal, spills and accidental exposure, and any other process where the GTMP is in use.
Naked DNA	DNA that is free in solution, not packaged in a vector.
Spill, major[a]	More than 5 mL or 5 g of a substance.
Spill, minor[a]	Less than 5 mL or 5 g of a substance.
Storage	Containment of a GTMP when it is not in use.
Reconstitution	The process of making the GTMP ready-to-administer. Also referred to as preparation (4).
Transportation	Movement of the GTMP around and/or between hospitals using hospital transport. NOT courier transport.

[a]Spill definitions are based on the definitions for major and minor spills of cytotoxic agents (5).

References

1. European Medicines Agency. Reflection paper on classification of advanced therapy medicinal products 2015 [updated 21 May 2015. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-classification-advanced-therapy-medicinal-products_en-0.pdf.
2. World Health Organization. Laboratory biosafety manual. 3 ed 2004.
3. Health and Safety Executive. Guidance on the use of genetically modified microorganisms in a clinical setting 2014 [updated 2014. Available from: https://www.hse.gov.uk/biosafety/gmo/acgm/acgmcomp/part6.pdf.
4. Pan UK Pharmacy Working Group for ATMPs. Gene therapy medicinal products: Governance and preparation requirements 2024 [updated February 2024. Available from: https://www.sps.nhs.uk/wp-content/uploads/2024/02/PAN-UK-PWG-for-ATMPs-Gene-Therapy-Guidance-V3.pdf.
5. University of British Columbia. Cytotoxic spill clean up 2021 [updated January 2021. Available from: https://riskmanagement.sites.olt.ubc.ca/files/2021/01/CHEM-SWP-004-Cytotoxic-Spill-Clean-Up.pdf.

Appendix 2. List of EC-approved GTMPs, as of January 2023 (1).

GTMP	Manufacturer	Indication	*in vivo/ ex vivo*	Viral vector	Biosafety level of vector[b] (2)
Glybera (alipogene tiparvovec)[a] (3)	uniQure biopharma	Familial lipoprotein lipase deficiency	*in vivo*	AAV-1	1
Imlygic (talimogene laherparepvec) (4)	Amgen/IDT Biologika	Unresectable, metastatic melanoma	*in vivo*	HSV-1	1/2[d]
Strimvelis[c] (5)	AGC Biologics	ADA-SCID	*ex vivo*	Retroviral	2
Yescarta (axicabtagene ciloleucel)[c] (6)	Kite Pharma	DLBCL, HGBL, PMBCL, FL	*ex vivo*	Retroviral	2
Kymriah (tisagenlecleucel)[c] (7)	Novartis	ALL, DLBCL, FL	*ex vivo*	Lentiviral	2
Luxturna (voretigene neparvovec) (8)	Spark Therapeutics/ Novartis	Inherited retinal dystrophy	*in vivo*	AAV-2	1
Zynteglo (betibeglogene autotemcel)[a,c] (9)	Minaris Regenerative Medicine	TDT	*ex vivo*	Lentiviral	2
Zolgensma (onasemnogene abeparvovec) (10)	Novartis/Alma c Pharma Services	5q SMA	*in vivo*	AAV-9	1
Libmeldy (atidarsagene autotemcel)[c] (11)	AGC Biologics	*ARSA*-mutant MLD	*ex vivo*	Lentiviral	2
Tecartus (brexucabtagene autoleucel)[c] (12)	Kite Pharma	MCL, ALL	*ex vivo*	Retroviral	2
Skysona (elivaldogene autotemcel)[a,c] (13)	Minaris Regenerative Medicine	*ABCD1*-mutant early cerebral adrenoleukody strophy	*ex vivo*	Lentiviral	2
Abecma (idecabtagene vicleucel)[c] (14)	Celgene	Multiple myeloma	*ex vivo*	Lentiviral	2
Breyanzi (lisocabtagene maraleucel)[c] (15)	Juno Therapeutics/ Celgene	DLBCL, PMBCL, FL	*ex vivo*	Lentiviral	2
Carvykti (ciltacaptagene autoleucel)[c] (16)	Janssen	Multiple myeloma	*ex vivo*	Lentiviral	2

Upstaza (eladocagene exuparvovec) (17)	MassBiologics South Coast/Almac Pharma Services	AADC deficiency	*in vivo*	AAV-2	1
Roctavian (valoctocogene roxaparvovec) (18)	BioMarin	Haemophilia A	*in vivo*	AAV-5	1
Hemgenix (etranacogene dezaparvovec) (19)	CSL Behring	Haemophilia B	*in vivo*	AAV-5	1

Please note this table is intended as a RESOURCE ONLY and DOES NOT REPLACE institutional risk assessment. The SmPC for individual products should always be consulted and local regulations should always be checked.

[a]Marketing authorisation not renewed.

[b]Biosafety level based on the Belgian classification (2); local classifications should be used where possible. Classification does not take into account the risk level of the transgene.

[c]Cellular product; may require additional training for appropriate handling (20).

[d]The Belgian classification classes HSV-1 as risk group 1 when used as a vector (2); however, the NIH guidelines for research involving recombinant or synthetic nucleic acid molecules classes all herpesviruses as risk group 2 (21). Consult local regulations for guidance.

Abbreviations: AADC, aromatic l-amino acid decarboxylase; AAV, adeno-associated virus; ADA-SCID, adenosine deaminase-severe combined immunodeficiency; ALL, acute lymphoblastic leukaemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HGBL, high-grade B cell lymphoma; HSV, herpes simplex virus; MCL, mantle cell lymphoma; MLD, metachromatic leukodystrophy; NIH, National Institutes of Health; PMBCL, primary mediastinal large B cell lymphoma; SMA, spinal muscular atrophy; TDT, transfusion-dependent beta-thalassaemia.

References

1. European Medicines Agency. CAT quarterly highlights and approved ATMPs 2023 [updated 29 January 2024. Available from: https://www.ema.europa.eu/en/documents/committee-report/cat-quarterly-highlights-approved-atmps-november-2023-january-2024_en.pdf.
2. Baldo A, van den Akker E, Bergmans HE, Lim F, Pauwels K. General considerations on the biosafety of virus-derived vectors used in gene therapy and vaccination. Current Gene Therapy. 2013;13:385-94.
3. GLYBERA Summary of Product Characteristics 2017 [updated 10 July 2017. Available from: https://www.ema.europa.eu/en/documents/product-information/glybera-epar-product-information_en.pdf.
4. IMLYGIC Summary of Product Characteristics 2022 [updated 22 November 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/imlygic-epar-product-information_en.pdf.
5. STRIMVELIS Summary of Product Characteristics 2022 [updated 08 July 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/strimvelis-epar-product-information_en.pdf.
6. YESCARTA Summary of Product Characteristics 2023 [updated 30 January 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf.
7. KYMRIAH Summary of Product Characteristics 2022 [updated 07 November 2022. Available from:

https://www.ema.europa.eu/en/documents/product-information/kymriah-epar-product-information_en.pdf.
8. LUXTURNA Summary of Product Characteristics 2023 [updated 04 May 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/luxturna-epar-product-information_en.pdf.
9. ZYNTEGLO Summary of Product Characteristics 2022 [updated 20 January 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/zynteglo-epar-product-information_en-1.pdf.
10. ZOLGENSMA Summary of Product Characteristics 2023 [updated 13 March 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_en.pdf.
11. LIBMELDY Summary of Product Characteristics 2023 [updated 17 April 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/libmeldy-epar-product-information_en.pdf.
12. TECARTUS Summary of Product Characteristics 2023 [updated 30 January 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/tecartus-epar-product-information_en.pdf.
13. SKYSONA Summary of Product Characteristics 2022 [updated 04 April 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/skysona-epar-product-information_en.pdf.
14. ABECMA Summary of Product Characteristics 2022 [updated 28 October 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/abecma-epar-product-information_en.pdf.
15. BREYANZI Summary of Product Characteristics 2022 [updated 08 April 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/breyanzi-epar-product-information_en.pdf.
16. CARVYKTI Summary of Product Characteristics 2023 [updated 14 April 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/carvykti-epar-product-information_en.pdf.
17. UPSTAZA Summary of Product Characteristics 2023 [updated 04 April 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/upstaza-epar-product-information_en-0.pdf.
18. ROCTAVIAN Summary of Product Characteristics 2022 [updated 09 November 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/roctavian-epar-product-information_en.pdf.
19. HEMGENIX Summary of Product Characteristics 2023 [updated 20 June 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/hemgenix-epar-product-information_en.pdf.
20. Pan UK Pharmacy Working Group for ATMPs. Gene therapy medicinal products: Governance and preparation requirements 2024 [updated February 2024. Available from: https://www.sps.nhs.uk/wp-content/uploads/2024/02/PAN-UK-PWG-for-ATMPs-Gene-Therapy-Guidance-V3.pdf.
21. National Institutes of Health. NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) 2019 [Available from: https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf.

Appendix 3. HSE 2007 guidance on containment measures required for GTMPs in a clinical research setting

Containment measure	Level 1	Level 2
Autoclave	Required on site	Required in the building
Access restricted to authorised personnel	Not required	Required
Measures to control aerosol dissemination	Not required	Required
PPE	Required	Required
Specified disinfection procedures	Required	Required
Safe storage of GTMP	Required	Required
Inactivation of GTMP in contaminated material and waste	Required by validated means	Required by validated means

'Level' refers to the containment level and not the biosafety level of the agents themselves. However, the risk group of the agent does correlate directly with the containment level, e.g., risk group 2 agents require containment level 2.
This table details the requirements from a containment perspective; additional precautions may be required to protect the product.
Abbreviations: GMTP, gene therapy medicinal products; UK Health and Safety Executive.

Appendix 4. Model for the roles and responsibilities for handling GTMPs

Handling stage	Chief pharmacist	Hospital pharmacy staff	Physician	Theatre/ward nurse	Biosafety officer[a]/hygiene services/infection control	Occupational health	Cleaners	Porters	Waste services
Initiation of GTMP treatment and setting up conditions, including environmental considerations	CI	CI	R	CI	CI	CI	CI	I	CI
Assessment: ability to handle, staff training[b]	R	S	RA		RS	S			
Screening GTMP prescriptions (patient basis)	R	RS	AC	CI	I[c]	I[c]			
Receipt of GTMP from the manufacturer and inspection	R	S	CI	CI	I[c]	I[c]			
Transportation	RA	S	CI	CI	SC	C		I	
Storage	R	S			SC	1			
Preparation and decontamination of biological safety device	R	SI			SC				
Dispensing	RA	S							
Administration (product-dependent)			R	RS					
Waste disposal	R	S	R	R	SC		S	S	S
Decontamination of GTMP spills	R[d]	R[d]S	R[d]	R[d]	ACI	CI	SI		
Accidental exposure	R[d]	R[d]	R[d]I	R[d]I	ACI	CI			

R, responsible person; A, person to whom 'R' is accountable; S, can be supportive; C, should be consulted; I, should be informed.

[a]In organisations where there is no appointed biosafety/infection control officer, the responsibilities should be taken by a member of the infection control body.

[b]Training will be limited to pharmacy training for pharmacists.

[c]Should be informed once at the start of the process when conditions for the use of GTMPs are being established.

[d]The person who spilled the GTMP, or was accidentally exposed, should be responsible for initiating the decontamination. Ultimate responsibility for ensuring the spill is appropriately decontaminated remains with the pharmacist.

Abbreviations: GMTP, gene therapy medicinal products.