CMC Considerations for Rare Disease and Personalised Therapies

Regulatory, analytical and manufacturing decision framework

UK • EU • US

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Regulatory changes	Modality landscape	LVV and LNP examples	Applying flexibility
What has changed across the UK, EU and US including frameworks that remain draft.	How viral and non-viral choices change the control strategy, evidence burden and development risks.	Where CMC precedent could create reusable knowledge across inputs, assays and process platforms.	Which activities can use prior knowledge and where product-specific evidence remains essential.

The discussion moves from regulatory change to modality-level application

Regulators are converging on proportionality

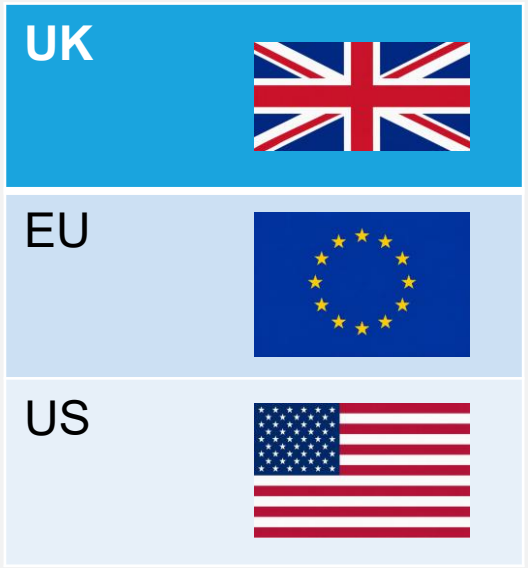
The opportunity is real, but several 2026 frameworks remain draft or consultation-stage.

Jurisdiction / date	Development	CMC implications	Status
US / Jan 2024	Final CAR-T guidance	Vector, cellular starting material, potency and comparability expectations	Implemented
EU / Jul 2025	Investigational ATMP guideline effective	Risk-based quality package across clinical development; lifecycle comparability	Implemented
UK / May 2026	Proposed Rare Disease Therapies Framework	Potential compressed development and Investigational Marketing Authorisation	Draft
US / Feb–Jun 2026	Individualised-therapy and genome-editing prior-knowledge drafts	Define invariant versus variant elements; justify bridging and residual uncertainty	Draft
US / May 2026	Final CGT CMC-flexibilities guidance	Use risk-based flexibility with early engagement and lifecycle commitments	Implemented
UK / Feb 2025	Draft guidance on individualised mRNA cancer immunotherapies	Define patient-specific variation and justify prior knowledge, with mRNA/LNP manufacturing controls and change control for product-design algorithms.	Draft
EU / Dec 2025 (proposal)	BioTech Act I	Potential reuse of common IMP quality documentation across trials, faster implementation would mean earlier CMC readiness	Legislative proposal
US/ Oct 2026	Rare Diseases Framework	Applies risk-based approaches, particularly to chemistry, manufacturing, and controls review and pre-approval inspections	Framework announcement

Developers must build a modular dossier, define invariant/variant elements, preserve patient–lot traceability, pre-agree comparability and explicitly carry residual uncertainty into follow-up.

Regulators are converging on proportionality

Global signals



Implemented guidance and emerging rare-disease and individualised therapy frameworks

Risk proportionate CMC

risk based assessment of prior knowledge, platform knowledge

Modular Evidence

Invariant vs variant elements

Lifecycle commitments

Comparability and residual uncertainty realities recognised

The modality landscape defines the evidence requirements

Ex vivo CAR-T is established; in vivo remains potential

Clinical maturity

7 FDA-licensed CAR-T products listed as of July 2026

Commercial precedent is overwhelmingly ex vivo; thus establishing a regulatory basis for platform knowledge and prior knowledge.

CMC risk remains key

- Patient-specific starting material and chain of identity
- Vector and cell-process variability
- Rapid release, potency and comparability
- Manufacturing failure affects an individual patient

In vivo moves the questions and the risks are more difficult to mitigate

- Delivery and tissue/cell targeting
- Dose control, persistence and repeat dosing
- Innate/adaptive immunogenicity
- Biodistribution and off-target activity

Lentiviral and γ-retroviral vectors integrate; recombinant AAV is predominantly episomal. Insertional-mutagenesis risk is dependent on the viral platforms.

Non-viral delivery changes the CMC challenge

Benefits

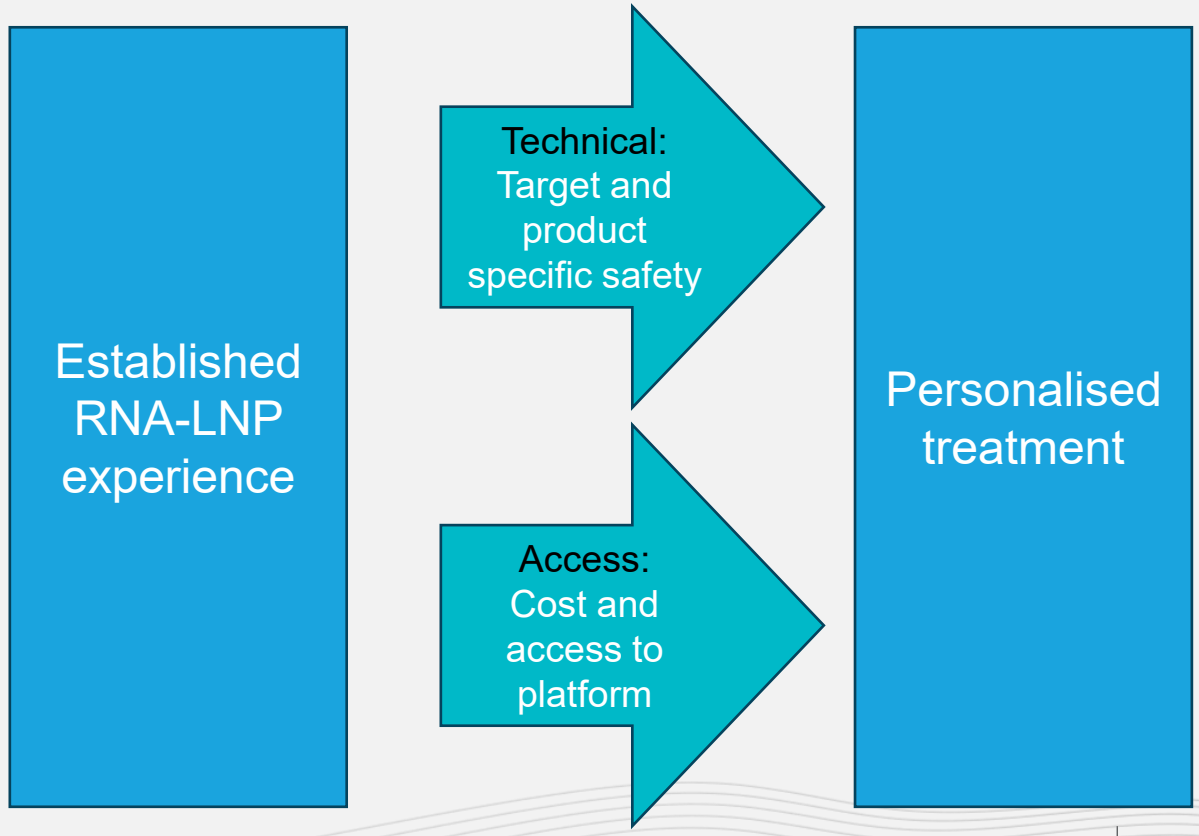
- Synthetic, modular inputs can support scale-up and shorter change cycles.
- Transient expression may be useful when reversibility is part of the safety strategy.
- Liposome/LNP and RNA-product experience provides relevant but necessarily interchangeable and used as prior knowledge.

What must be controlled

- Lipid identity, purity, ratios and degradants
- Particle size/distribution, morphology and encapsulation
- RNA/editor identity, integrity, capping/poly(A) and potency
- Stability, container closure and in-use handling

Further development required

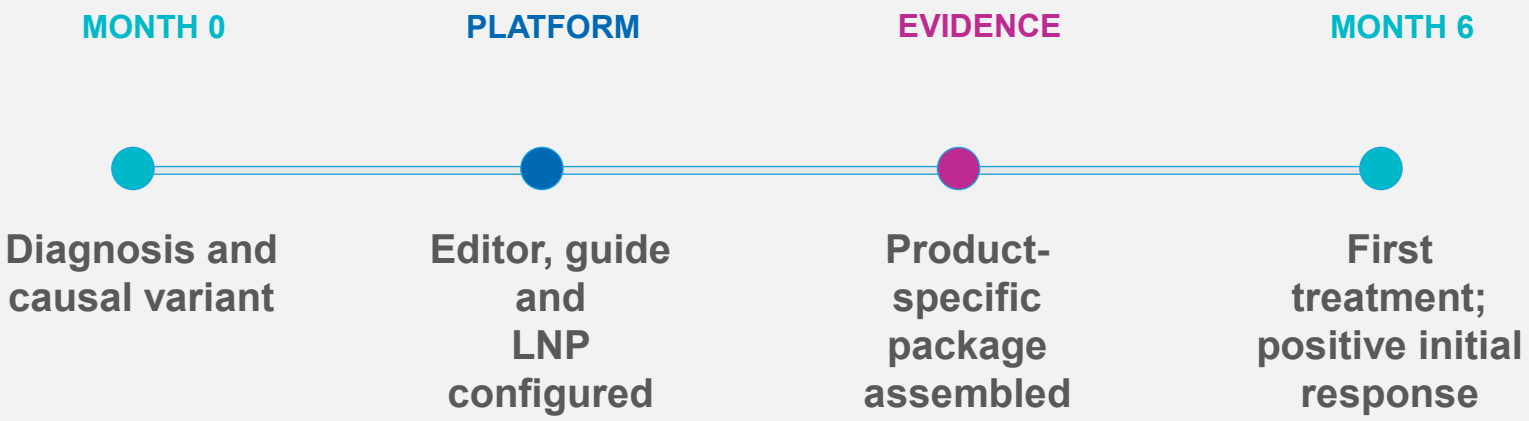
- Cell- and tissue-selective delivery
- Innate immune activation and liver exposure
- Repeat dosing and anti-component immunity
- Durability versus the intended clinical mechanism



For more information, please read https://www.wypartnership.co.uk/application/files/3716/4735/6437/making-information-accessible-for-neurodivergent-people-final-v2-20.04.21.pdf

Baby KJ proves speed and provides a clear example

Personalised in vivo CRISPR-based treatment for CPS1 deficiency; diagnosis to first treatment in six months.



NIH describes the first known single-patient personalised CRISPR medicine and a positive initial response.

Invariant platform elements may support prior knowledge across programs if comparability and relevance are demonstrated.

FDA's June 2026 draft explicitly discusses leveraging public and platform knowledge for genome-editing CMC, nonclinical and clinical packages. **Public evidence and shared regulatory experience can reduce duplication, while proprietary technology access and product-specific development remain important barriers.**

Baby KJ project - useful outputs

- Detailed scientific description of the science behind the therapy and its development
- Second paper describing the potential regulatory structure that would support other treatments under this treatment umbrella
- pre-IND briefing books and FDA responses for the urea-cycle-disorder base-editing programme, as well as related programmes
- Type B, pre-IND Meeting Request (UCDs Base Editing Program)

The KJ experience helped inform a wider regulatory discussion on personalised therapies, reflected in FDA's 2026 draft Plausible Mechanism Framework.

SCGE Platform - IND Resources - https://scge.mcw.edu/platform/data/ind/resources

Clinical precedent can create reusable CMC knowledge

Among emerging direct in vivo gene therapy modalities relevant to rare and individualised diseases, LNP and LVV are two clear candidates for platform-based CMC development.

Therapy type	Clinical precedent	Suggested reusable CMC elements
In vivo LVV	Small, emerging clinical set	Vector backbone; producer cells; plasmids; upstream/downstream process; titre, RCL and impurity assays
In vivo LNP genome editing	Large and expanding set	Ionisable/helper lipids; RNA/editor/guide manufacture; mixing; particle and cargo assays; biodistribution
In vivo LNP mRNA therapy	Established repeat-dose clinical set	mRNA platform; lipid system; encapsulation; expression potency; stability; repeat-dose knowledge
Targeted LNP cell programming	Early but rapidly expanding	Targeting ligand; targeted particle attributes; cell uptake; expression potency; off-target cell transfection
AAV gene therapy	Large clinical precedent	Capsid-specific process and assays; genome integrity; potency; biodistribution; immunogenicity
Antibodies / recombinant proteins	Very large precedent	Cell line; upstream/downstream platform; formulation; standard release and stability methods

in vivo LVV + non-viral LNP. Potential knowledge generation, not automatic regulatory platform designation or interchangeability.

Lentiviral vectors: reuse must be justified layer by layer

In vivo LVV: a small clinical set with high platform relevance

I performed an indicative search using GlobalData to create a working inventory.

This was interrogated to understand the number of the therapies in development based on a search of clinical trial data bases.

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strongly supported by primary or equivalent public evidence

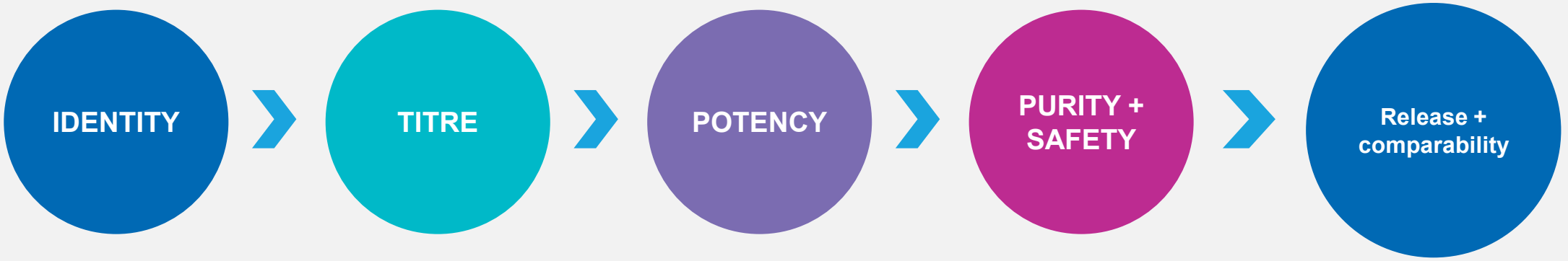
Named programmes in the working inventory

INT2104 • ESO-T01 • KLN-1010 • UB-VV111 • UB-VV400 • UB-VV410 • JY-231 • JY-232 • LB-2501 • SL-1617 • KXV-01 • LV-009 • KIV-318 • CIB in vivo CAR-T • VV-169 • V-001 • Kv1.1 epilepsy LVV • BI 3720931 • ProSavin • OXB-102 • RetinoStat • SAR422459 • SAR421869

Platformable layer	Recurring elements across programmes
Vector / starting materials	SIN backbone; envelope / targeting ligand; transfer and helper plasmids; producer cell substrate
Manufacturing process	Transfection or stable production; harvest; nuclease treatment; clarification; TFF / chromatography; formulation and fill
Analytics	Identity and genome integrity; physical and infectious titre; potency; RCL; HCP / hcDNA; plasmid and nuclease residuals
Disposition / safety	Biodistribution; persistence; shedding; integration-site analysis; non-target transduction; long-term follow-up
Lifecycle knowledge	Reference standards; stability; scale / site comparability; process validation and impurity-clearance knowledge

Viral analytics must link titre and potency

An orthogonal evidence chain connects vector identity and quantity to biological function and safety



Reference standards, stability-indicating methods and lifecycle comparability keep the chain intact.

Vector-specific risks matter: integrating vectors, for example, require insertional-mutagenesis controls.

LVV reuse is strongest in stable inputs, assays and process platforms

Prior knowledge can narrow repeat work, but it cannot replace product-specific potency, comparability or safety evidence.

Reusable platform layer	Work potentially reduced	Product-specific evidence retained
Inputs and substrates	Reuse qualified packaging/helper plasmids, fixed backbone knowledge and producer-cell-bank packages.	Bridge transgene/promoter changes; retain identity, purity, traceability and change-control evidence.
Assays and controls	Transfer RCL, compendial safety, HCP/hcDNA and titre method frameworks instead of developing them de novo.	Show matrix suitability, transgene-specific performance, reference-standard control and potency relevance.
Process and lifecycle	Start from proven upstream ranges, AEX/TFF/benzonase steps, clearance knowledge, formulation/CCIT and stability models.	Confirm scale/site performance and comparability; justify PPQ flexibility; continue real-time stability.

Lipid nanoparticles: broad precedent, product-specific controls

Established materials, methods and process design space can accelerate development without replacing payload-specific evidence.

Non-viral LNP: broad clinical precedent across reusable platform layers

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initially retained by explicit LNP or recognised programme screen

Representative programme families

NTLA / nex-z / lonvo-z • VERVE • BEAM • CTX • YOLT • Moderna mRNA • ARCT / LUNAR • ReCode • Vertex / Moderna • BioNTech • Precision • Tessera • targeted tLNP programmes

Platformable layer	Recurring elements across programmes
Lipids / excipients	Ionisable lipid; helper phospholipid; cholesterol; PEG-lipid; lipid identity, purity, ratios and degradants
Cargo manufacture	DNA template; IVT enzymes; mRNA / guide identity, integrity, capping, poly(A), dsRNA and truncates
Particle process	Mixing / assembly; flow-rate and ratio controls; purification; concentration; sterile filtration; fill-finish
Particle analytics	Size / PDI; morphology; encapsulation; free cargo; lipid content; pH / osmolality; residual solvent
Biological performance	Cell uptake; endosomal escape; expression, editing or silencing potency; innate immune activation
Lifecycle evidence	Biodistribution; repeat dosing / anti-component immunity; stability; container closure; scale / site comparability

For more information, please read https://www.wypartnership.co.uk/application/files/3716/4735/6437/making-information-accessible-for-neurodivergent-people-final-v2-20.04.21.pdf

LNP reuse is strongest in materials, analytical methods and process design space

Established mRNA/LNP controls provide a faster starting point; every cargo and formulation still needs a justified control strategy.

Reusable platform layer	Work potentially reduced	Product-specific evidence retained
Materials and cargo	Reuse lipid supplier packages, IVT-enzyme controls and unchanged plasmid-backbone knowledge.	Assess changed lipid chemistry, coding sequence, UTR/poly(A), payload purity and formulation-specific risks.
Analytical platform	Transfer particle size/PDI, encapsulation, lipid content, mRNA integrity/capping and impurity method frameworks.	Confirm payload matrix, sequence/length effects, specification suitability and product-specific reference standards.
Process and lifecycle	Use established mixing design space, TFF, sterile-filtration, degradant, stability and container knowledge.	Confirm CQAs at scale, filtration validation, formulation performance, potency, real-time stability and CCIT.

distinguish reusable method for architecture and possibly formulation from payload specific acceptance criteria.

Flexibility depends on platform discipline—not reduced product understanding

What changed

- Regulators increasingly permit risk-based use of prior and platform knowledge.
- Define invariant versus variant elements and explain the bridge.
- Treat draft and final frameworks according to their status.

Where to use it

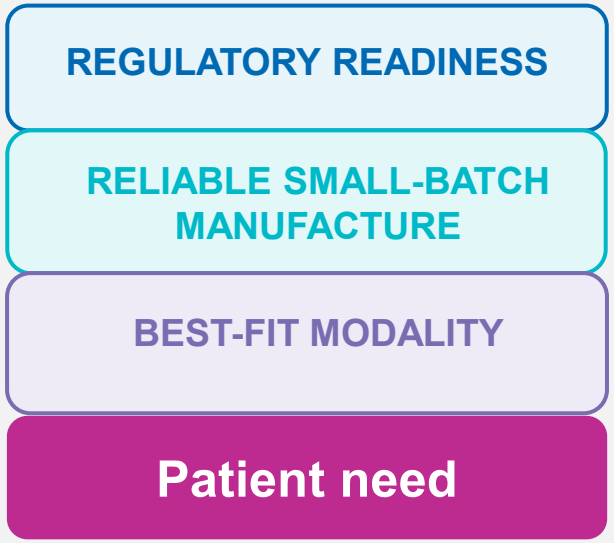
- LVV: stable inputs, assay frameworks and transferable process knowledge.
- LNP: materials, analytical methods and established process design space.
- Use comparability to focus new work on what actually changed.

What remains specific

- Potency and mechanism-linked acceptance criteria.
- Biodistribution, off-target exposure, immunogenicity and persistence.
- Patient–lot traceability, residual uncertainty and lifecycle follow-up.

Science will determine the modality; regulatory flexibility can help it reach the patient

A modality-agnostic development system can be ready for small-batch and personalised medicines.



Science determines the modality.

LVV understanding Stronger identity, purity and potency knowledge can improve process control, comparability and cost.

Non-viral reach Greater specificity and clearer on/off-target understanding can broaden eligible tissues and diseases.

Patient access Platform knowledge, standardisation and automation can shorten repeated development and time to treatment and potentially reduce costs

Concluding remarks

Greater regulatory flexibility still leaves a gap in patient access

Regulation is adapting	Conventional development models fit rare and personalised therapies poorly. Regulators are moving towards greater flexibility, but remain unevenly aligned.
Science leads	Frameworks are catching up with innovation, extending the science- and risk-based thinking used for ATMPs beyond conventional biologics.
Platforms create opportunity	Large companies and platform holders can use accumulated CMC knowledge to reduce repeated work, while retaining product-specific evidence.
The divide remains	Academic developers bring scientific innovation. Pharma and CDMOs hold much of the manufacturing and commercial capability. High costs and fragmented regulation keep them apart.

The challenge is to connect academic innovation with affordable platforms that can deliver personalised and ultra-rare therapies.

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