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RETHINKING EXTRACTABLES AND LEACHABLES RISK FOR ADVANCED THERAPEUTIC MEDICINAL PRODUCTS (ATMPs)

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ABSTRACT
Extractables and leachables (E&L) science has matured over three decades around a relatively narrow product archetype: small-molecule drugs, monoclonal antibodies, and conventional vaccines formulated in stable, well-characterized matrices and assessed primarily against systemic toxicological endpoints. Advanced Therapeutic Medicinal Products (ATMPs) — CAR-T and other engineered cell therapies, in vivo and ex vivo gene therapies, CRISPR-based editing products, exosomes and other extracellular vesicles, mRNA-lipid nanoparticle (LNP) constructs, organoids, and complex cell culture media — do not fit this archetype. Their critical quality attributes are not merely chemical purity and systemic safety margins but *biological function*: potency, transfection or transduction efficiency, immune quiescence or activation, genome-editing fidelity, and structural integrity of nanoscale or supramolecular assemblies. This review critically examines whether the toxicological logic underpinning current E&L thresholds — the Threshold of Toxicological Concern (TTC), Permitted Daily Exposure (PDE), and Analytical Evaluation Threshold (AET) — remains scientifically defensible for living-cell and nanoparticulate products, and proposes a next-generation, function-first risk assessment framework tailored to the biology of ATMPs.
Graphical Abstract: **Figure**

KEYWORDS: Extractables and Leachables (E&L); Advanced Therapy Medicinal Products (ATMPs); Risk Assessment; Biocompatibility; Pharmaceutical Packaging; Single-Use Systems; Patient Safety; Chemical Characterization; Toxicological Risk Assessment; Regulatory Compliance.

1. INTRODUCTION: The Legacy Paradigm

Modern E&L risk assessment is built on a coherent, if narrow, logic. ICH Q3D, USP <1663>/<1664>, and the Product Quality Research Institute (PQRI) safety thresholds all converge on a single conceptual move: convert a chemical's identity and daily intake into a probability of systemic toxicological harm, then set an analytical reporting/qualification threshold below which that probability is judged negligible. The TTC concept (commonly anchored around 1.5 µg/day for an unstudied organic impurity of unknown structure) and PDE-based limits derived from no-observed-adverse-effect levels (NOAELs) with uncertainty factors are fundamentally *dose-response toxicology* tools. They were calibrated using datasets built almost entirely from small-molecule pharmacology and, more recently, extended by analogy to biologics such as monoclonal antibodies (mAbs) and inactivated or subunit vaccines.[1]

This extension was defensible for mAbs and vaccines because, despite their biological origin, the *risk logic* stayed essentially systemic-toxicological: a leachable is a

foreign chemical entity that reaches the patient's bloodstream and may cause organ toxicity, genotoxicity, or hypersensitivity. The mAb or vaccine antigen itself was treated as inert to the leachable at the concentrations typically encountered — a reasonable assumption for a robust, relatively concentration-insensitive protein in a well-buffered formulation.[2]

ATMPs break this assumption in ways that are not incremental but categorical. The "product" in a CAR-T therapy is not a molecule in a vial; it is a population of living, metabolically active, epigenetically plastic human cells whose fate is partially undetermined at the point of administration. The "product" in an mRNA-LNP vaccine is a self-assembled nanoparticle whose lipid packing order, apparent pKa, and surface charge are the entire mechanism of action. In both cases, a leachable does not merely need to avoid poisoning the patient — it must avoid poisoning, activating, silencing, or subtly reprogramming the therapeutic entity itself, often at concentrations far below any threshold a systemic toxicology framework would flag.[3]

2. Why ATMPs Are Mechanistically Different

2.1 Living cells as both drug substance and drug product

In cell and gene therapies, the manufacturing process — apheresis, activation, viral transduction, expansion, formulation, cryopreservation — brings the cellular product into contact with an extensive materials footprint: bioreactor bags and tubing, chromatography resins, tangential flow filtration membranes, cryobags, closed-system connectors, and final fill containers. Unlike a purified protein, cells actively metabolize, transport, and respond to their chemical environment. A plasticizer or antioxidant leachable that is toxicologically silent at nanomolar concentrations in a rodent liver panel may nonetheless:

- Bind intracellular receptors (e.g., aryl hydrocarbon receptor ligands common among process-related leachables) and alter T-cell differentiation trajectories.
- Perturb mitochondrial membrane potential in a way that is invisible to standard cytotoxicity (MTT/LDH) assays but measurably reduces exhaustion resistance or persistence potential.
- Act as low-level danger-associated molecular pattern (DAMP) mimetics or adjuvant-like species that shift T-cell or NK-cell activation state before the product ever reaches the patient.[4]

2.2 Immune activation as an intrinsic sensitivity, not an adverse event category

Traditional E&L toxicology treats immunogenicity as one adverse outcome among several (alongside genotoxicity, carcinogenicity, reproductive toxicity), assessed largely through sensitization thresholds. For ATMPs, immune activation is not a peripheral safety endpoint — it is frequently the *primary pharmacology*. A leachable that engages pattern recognition receptors (TLRs, NLRP3 inflammasome components) at concentrations orders of magnitude below any systemic PDE can:

- Trigger premature or excessive activation of CAR-T cells during ex vivo manufacturing, driving terminal differentiation and reduced in vivo persistence.
- Act as an unintended adjuvant for viral vector capsid proteins, amplifying anti-AAV or anti-lentiviral neutralizing antibody responses and compromising re-dosing potential or long-term transgene expression.
- Prime innate immune sensors against mRNA-LNP constructs, increasing reactogenicity independent of the mRNA payload itself.

None of these mechanisms require the leachable to cross a systemic toxicity threshold. They require only that it perturb a receptor-mediated signaling cascade — a fundamentally lower-dose, higher-sensitivity phenomenon than organ toxicity.[5]

2.3 Transfection and transduction efficiency as a leachable-sensitive endpoint

For non-viral gene delivery (LNP-mRNA, LNP-siRNA, polymeric nanoparticles), transfection efficiency depends on a cascade of physicochemical events: nanoparticle self-assembly, colloidal stability, endosomal uptake, pH-triggered endosomal escape via ionizable lipid protonation, and cytosolic payload release. Each step is exquisitely sensitive to trace chemical perturbation:

- Surfactant-like leachables (common from single-use bioprocessing films, e.g., oleamide, Irgafos degradants, or residual biocides) can competitively insert into the lipid bilayer, altering the apparent pKa of ionizable lipids and blunting endosomal escape efficiency by an order of magnitude — with no signal on any chemical purity assay of the drug product itself.[6]
- Trace metal leachables (from stainless steel, filter housings) can catalyze lipid peroxidation within the LNP, degrading structural integrity during shelf life in a way invisible to release-testing potency assays performed on fresh material.
- Divalent cation contamination can alter mRNA secondary structure or nanoparticle surface charge, shifting biodistribution and cellular uptake kinetics.[7]

2.4 Viral vector potency and capsid integrity

AAV and lentiviral vectors are proteinaceous nanoparticles whose infectivity depends on capsid conformational integrity and surface charge distribution for receptor engagement. Extractables that are chemically unremarkable — low-molecular-weight siloxanes from tubing, residual sterilizing agents, or oxidative species generated by gamma-irradiated single-use components — can:

- Oxidize surface-exposed capsid residues, reducing receptor-binding affinity and transduction titer without altering total particle count (a discrepancy

between physical and infectious titer that is a well-recognized but poorly root-caused phenomenon in the field).
- Promote capsid aggregation, which both reduces effective dose and increases innate immune recognition (aggregated proteins are potent complement and TLR activators).[8]

2.5 Organoids, iPSC-derived products, and cell culture media

Organoids and iPSC-derived therapeutics are defined by multi-week differentiation trajectories in which small molecule signaling (Wnt, BMP, Notch, retinoic acid pathways) is precisely tuned. A leachable with even weak endocrine-disruptor-like activity (e.g., phthalates, bisphenol analogs migrating from culture-ware) can act as a low-affinity but chronically present agonist or antagonist at nuclear hormone receptors that overlap with differentiation-controlling pathways, skewing lineage commitment over the culture period — an effect with no analog in the single-exposure toxicology models that underpin PDE derivation.[9]

3. Critical Evaluation: Do Current Toxicological Concepts Remain Valid?

3.1 The TTC/PDE framework assumes the wrong dose-response shape

TTC and PDE values are built on *monotonic, threshold-type dose-response toxicology* — the assumption that below some NOAEL-derived value, no adverse biological effect occurs, scaled by uncertainty factors for interspecies and interspecies variability. Receptor-mediated immunomodulatory and membrane-partitioning phenomena, however, frequently display **non-monotonic dose-response (NMDR)** behaviour, well documented in the endocrine-disruptor literature: low concentrations can produce effects that intermediate or high concentrations do not, because different mechanisms (receptor binding versus receptor saturation/desensitization or cytotoxic overload) dominate at different concentration ranges. A framework calibrated to detect harm only above a monotonically increasing curve is structurally blind to NMDR effects that may be biologically dominant for ATMP-relevant endpoints.[10]

3.2 The endpoint mismatch problem

PDE derivation is endpoint-specific to organ toxicity, genotoxicity, and carcinogenicity — endpoints chosen because they are what a systemically administered small molecule or protein is expected to cause. ATMP-relevant harms (loss of potency, altered persistence, reduced editing fidelity, immune priming, nanoparticle destabilization) are not represented in *any* toxicological database used to derive TTC values. There is, quite simply, no NOAEL for "20% reduction in CAR-T central memory phenotype" or "15% loss of endosomal escape efficiency." Applying a threshold derived from one endpoint category to protect against an entirely different, mechanistically unrelated endpoint category is a category error, not a conservative extrapolation.[11]

3.3 Dose accumulation logic does not transfer

PDE calculations assume systemic, whole-body distribution and typically integrate exposure over a lifetime or a defined treatment duration, with the liver, kidney, or other organs as the target. For ex vivo-manufactured cell products, the "exposure" of concern occurs during a finite manufacturing window (days) at the *local, cellular microenvironment* level — concentrations in a bioreactor or cryobag are not diluted across a 70 kg body but act directly on the cells in contact with the leachable-bearing surface. The dose metric itself (mass/day/patient) is arguably the wrong unit; local concentration at the cell-material interface, exposure duration during culture, and even the developmental/activation state of the cell at the time of exposure are more mechanistically relevant.[11]

3.4 The analytical evaluation threshold assumes irrelevance of trace species — an increasingly untenable assumption

The AET is set based on analytical detectability and the toxicological safety threshold, explicitly *not* on biological activity. For potency-sensitive, receptor-driven, or self-assembly-dependent products, a chemical species can be biologically highly potent (nanomolar receptor affinity, or sufficient to disrupt colloidal assembly) while remaining well below any AET calculated for systemic safety. The implicit assumption that "if it's too dilute to see, it's too dilute to matter" does not hold when the target of concern is a receptor-mediated or self-assembly-dependent process rather than bulk-tissue toxicology.[12]

3.5 Where the legacy framework remains valid

It would be an overcorrection to discard systemic toxicological thresholds entirely. For ATMPs administered systemically with a defined pharmacokinetic exposure to leachables reaching circulation (e.g., leachables from an IV administration set delivering a cell suspension), classical organ-toxicity endpoints and PDE-style thresholds remain relevant and necessary — they simply are not *sufficient*. The correct critique is not "TTC/PDE are wrong" but "TTC/PDE address only one of several risk domains relevant to ATMPs, and are frequently the least sensitive one for product-intrinsic harm."[13]

4. Toward a Next-Generation, Function-First Risk Assessment Framework

The core proposal of this review is a shift from a **single-threshold, chemistry-only paradigm** to a **multi-domain, function-anchored paradigm** in which chemical characterization is necessary but not sufficient, and biological/functional readouts are elevated to co-primary risk metrics.[14]

4.1 Domain-based risk stratification

Rather than a single AET/PDE gate, ATMP E&L risk should be evaluated across at least four semi-independent domains, each with its own relevant threshold logic:

1. **Systemic toxicological domain** — retains classical TTC/PDE logic, applied where systemic patient exposure to leachables is plausible (e.g., direct IV lines, excipients in final formulation).
2. **Product-functional domain** — potency, transduction/transfection efficiency, editing fidelity, differentiation trajectory fidelity, assessed via matched functional assays performed on product exposed to worst-case leachable profiles versus unexposed controls.[15]
3. **Immunomodulatory domain** — innate and adaptive immune activation signatures (cytokine release, TLR/NLRP3 reporter activation, complement activation, dendritic cell maturation markers) assessed independently of systemic toxicology, given the NMDR concerns above.
4. **Biophysical/structural domain** — for nanoparticulate and vector-based products, assessment of particle size distribution, zeta potential, capsid integrity (by orthogonal methods such as cryo-EM, DSC, or receptor-binding assays), and colloidal stability under leachable challenge.[16]

A leachable that clears the systemic domain but fails the functional, immunomodulatory, or biophysical domain should trigger the same regulatory and mitigation response as a classical toxicological failure — the framework must treat "loss of function" and "gain of unwanted immune signal" as first-class safety findings, not secondary quality observations.[17]

4.2 Matrix-relevant, worst-case simulation studies over generic extraction protocols

Standard extraction studies (using ethanol, water, and other model solvents at elevated temperature) are designed to maximize chemical recovery for toxicological cataloguing. They are poorly suited to reproducing the actual physicochemical microenvironment a leachable will encounter — cell culture media, ionic strength, protein content, pH, and shear all modulate leachable behavior and bioavailability to the product. Product-representative simulation studies, using actual process fluids/media and process-representative contact conditions (temperature, duration, agitation), should be the default for ATMP E&L, with generic solvent-based extractables studies retained only for initial chemical hazard identification.[18]

4.3 Orthogonal functional and reporter-based bioassays as routine screening tools

A next-generation framework should incorporate a tiered battery of rapid, sensitive functional bioassays as routine leachable-impact screens, including:

- Reporter cell lines for TLR2/4, NLRP3 inflammasome, and NF-κB activation, to flag immunomodulatory leachables independent of identity.
- Endosomal escape reporter systems (e.g., galectin-recruitment or split-GFP complementation assays) for LNP/mRNA products, to directly measure functional impact rather than inferring it from particle size alone.
- Potency-matched cell activation/exhaustion marker panels (e.g., PD-1/TIM-3/LAG-3 expression, central memory phenotype retention) for cell therapy products exposed to candidate process materials.
- Vector infectivity/transduction titer ratios (physical:infectious particle ratio) as a sensitive, integrated readout of capsid-level leachable impact.

These assays are individually established in adjacent fields (immunotoxicology, nanomedicine characterization) but are rarely integrated into E&L risk assessment workflows, which remain dominated by analytical chemistry (GC-MS, LC-MS, ICP-MS) divorced from functional readout.[19]

4.4 Material and process risk scoring integrated with Quality by Design (QbD)

Rather than testing final products against a universal threshold, material qualification should shift upstream: single-use systems, media components, and container-closure materials should be scored on a Critical Material Attribute (CMA) basis specific to the ATMP modality, informed by structure-based hazard flags (known endocrine-disruptor chemotypes, known TLR agonist chemotypes, redox-active species) even before empirical leachable data exists. This aligns E&L risk assessment with the broader QbD and Process Analytical Technology (PAT) movement already established for biologics manufacturing, but extends the "critical quality attribute" concept explicitly to include immunological and functional attributes of process materials, not just chemical purity.[20]

4.5 Read-across and computational prioritization

Given the combinatorial scale of material-product combinations in cell and gene therapy manufacturing (dozens of single-use components × dozens of leachable species × multiple modalities), empirical functional testing of every combination is infeasible. A pragmatic framework should use structure-activity relationship (SAR) and read-across approaches — informed by existing endocrine-disruptor, immunotoxicology, and membrane-partitioning (log P/log D-based) databases — to prioritize which leachable-material-modality combinations warrant full functional bioassay investment, reserving exhaustive testing for high-prior-probability hazards (e.g., known TLR agonist chemotypes, surfactant-like species with membrane-partitioning potential).[22]

4.6 Modality-specific thresholds, not a universal AET

The framework should explicitly abandon the goal of a single universal AET for all ATMPs, replacing it with modality-informed threshold setting: LNP-based products should have leachable limits informed by demonstrated no-effect concentrations on endosomal escape and colloidal stability; cell therapies should have limits informed by no-effect concentrations on

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activation/exhaustion marker panels during the actual manufacturing exposure window; viral vector products should have limits informed by no-effect concentrations on infectivity ratio and capsid integrity. This is analogous to how ICH Q3D already differentiates PDEs by route of administration — the same logic should be extended to differentiate thresholds by *mechanism of therapeutic action*, not only by route.

4.7 Regulatory and lifecycle considerations

Regulators (FDA CBER, EMA CAT) have acknowledged in guidance discussions and workshops that existing E&L paradigms were not designed with cell and gene therapies in mind, but formal, modality-specific guidance remains underdeveloped relative to the pace of ATMP approvals. A next-generation framework should be paired with:

- Explicit regulatory acceptance of functional/immunomodulatory bioassay data as part of the E&L risk assessment package, alongside chemical characterization.
- Lifecycle-stage-appropriate rigor: extensive functional screening at material/process selection and design-space definition, with confirmatory (not exhaustive) testing at commercial validation, consistent with QbD principles.
- Cross-industry data-sharing consortia (building on precedents such as the BioPhorum Operations Group's work on extractables for biologics) to build the modality-specific hazard databases that read-across approaches in Section 4.5 depend on — no single sponsor can generate this evidence base alone.[23]

The next-generation E&L program should explicitly connect leachables to critical quality attributes. A useful matrix is where E&L becomes integrated into the overall control strategy rather than remaining an isolated toxicology exercise.

Leachable effect	Process impact	Potential CQA impact	Clinical relevance
Cytotoxicity	Cell loss	Viability	Safety/efficacy
Growth inhibition	Reduced expansion	Cell number/potency	Efficacy
Activation	Altered phenotype	Phenotype/cytokines	Safety/efficacy
Mitochondrial dysfunction	Metabolic stress	Potency/viability	Efficacy
Membrane interaction	Vector/LNP instability	Particle integrity	Efficacy
Oxidative chemistry	RNA/protein damage	Molecular integrity	Efficacy/safety
Surface adsorption	Product loss	Recovery/concentration	Dose accuracy
Immune stimulation	Cytokine response	Functional phenotype	Safety/efficacy

5. Proposed integrated framework: Beyond chemical safety

5.1. Domain 1: Chemical characterization

Chemical characterization involves identifying potential material-derived compounds that may be released from materials used in the manufacturing and processing of Advanced Therapy Medicinal Products (ATMPs). It includes determining the chemical identity and concentration of detected compounds using appropriate analytical techniques. The assessment should also consider analytical uncertainties, method limitations, detection capabilities, and any challenges associated with the identification and quantification of extractables and leachables (E&L).

5.2. Domain 2: Toxicological qualification

Toxicological qualification focuses on estimating potential patient exposure to identified leachable compounds under relevant conditions of product use. The toxicological risks of individual compounds should be evaluated using available toxicological data, applicable safety thresholds, and exposure-based risk assessment principles. Based on the estimated exposure and toxicological significance, appropriate exposure limits and risk-control measures should be established to ensure patient safety.

5.3. Domain 3: Biological compatibility

Biological compatibility assessment evaluates the potential effects of material-derived compounds on the biological integrity and functionality of ATMPs. This includes assessing possible impacts on cellular viability, cell identity, potency, stability, and other relevant product quality attributes, as well as vector integrity and functionality where applicable. Product-specific biological acceptance criteria should be established to ensure that contact materials and their associated leachables do not adversely affect product quality, safety, or efficacy.

Integrated ATMP Extractables and Leachables (E&L) Risk Assessment Framework

An integrated ATMP E&L risk assessment framework can be developed by combining chemical characterization, toxicological qualification, and biological compatibility into a unified evaluation approach. This framework considers the chemical identity and concentration of material-derived compounds, the potential patient exposure and associated toxicological risks, and the possible effects of these compounds on the biological integrity and quality of the final product. These assessment domains should be supported by process-specific controls that account for manufacturing conditions, material-contact duration, product characteristics, and relevant clinical applications. The proposed framework provides a systematic approach to identifying, evaluating, and controlling E&L-related risks throughout ATMP manufacturing.

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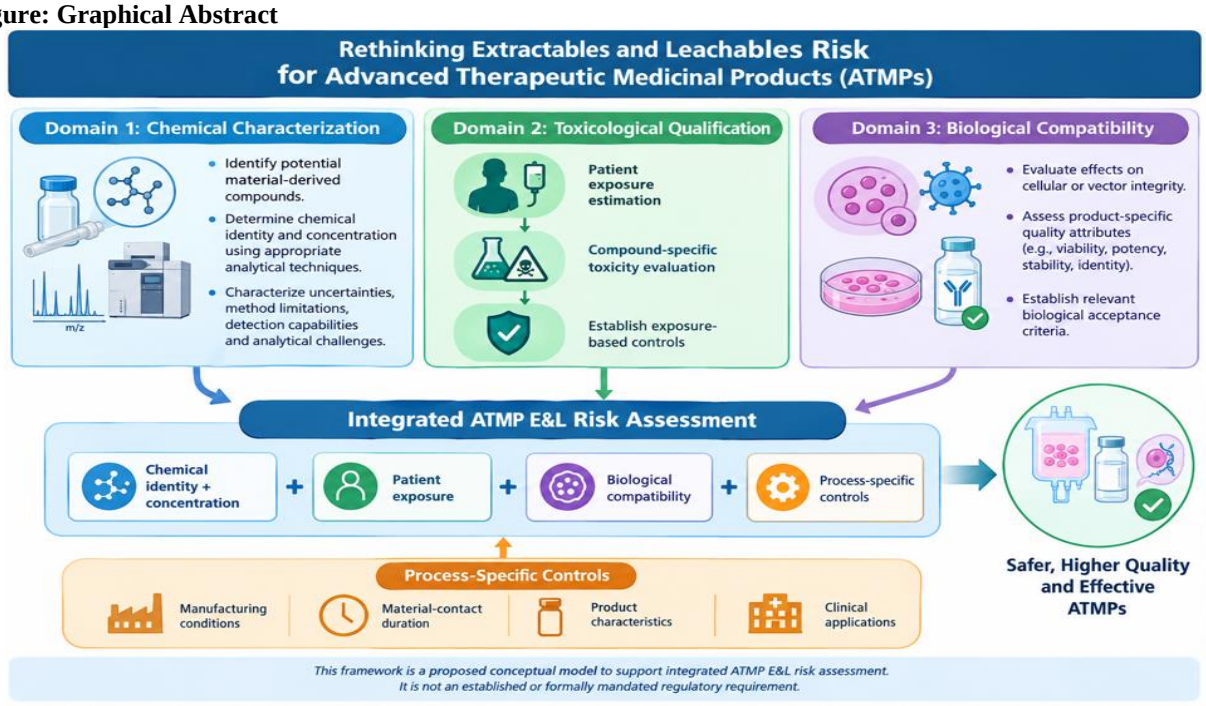
6. Regulatory framework and standards

Guideline or standard	Relevance to the review
ICH Q3E	Holistic framework for E&L assessment and control; draft guideline
ICH Q9(R1)	Quality risk-management principles
USP	Extractables assessment for pharmaceutical packaging systems
USP	Leachables assessment for pharmaceutical packaging systems
USP	Plastic components and systems used in pharmaceutical and biopharmaceutical manufacturing
ISO 10993-18	Chemical characterization of medical device materials; relevant where applicable to device-related components
FDA guidance on CGT materials	Material qualification and safety considerations for cell and gene therapy manufacturing
USP	Characterization and qualification of plastic components and systems used in pharmaceutical manufacturing

Figure: Graphical Abstract



7. DISCUSSION: Reframing "Safety" for Living Therapeutics

The deepest conceptual shift this review argues for is a redefinition of what "safety" means in the E&L context for ATMPs. Classical E&L risk assessment answers the question: *does this leachable harm the patient?* For living, functionally defined therapeutics, an equally important and mechanistically distinct question is: *does this leachable harm the therapy?* A CAR-T product rendered inert by premature exhaustion, an AAV vector with a ten-fold reduction in infectious titer, or an mRNA-LNP with degraded endosomal escape efficiency may pose no direct systemic toxicity risk at all — and yet represents a patient safety failure of the first order, because the patient receives a product that does not work, often in a one-time, non-repeatable, or resource-intensive treatment context where therapeutic failure carries irreversible consequences.

This reframing does not diminish the importance of classical toxicology; it situates it as one necessary but insufficient pillar within a broader, biology-literate risk architecture. The chemistry-first, threshold-driven paradigm that has served small-molecule and conventional biologic products well for decades was never designed to answer questions about receptor-mediated immune priming, non-monotonic dose-response, nanoparticle self-assembly, or living-cell phenotype drift — and it should not be retrofitted by analogy alone to do so.

The regulatory direction appears increasingly compatible with a science- and risk-based model rather than a purely prescriptive one. The draft ICH Q3E framework is explicitly intended to establish a holistic approach to E&L assessment and control. At the same time, the regulatory framework for ATMPs increasingly emphasizes product-specific quality and potency. EMA's current guideline for investigational ATMPs covers

quality, non-clinical and clinical considerations across gene therapy, cell therapy and tissue-engineered products. FDA's current cellular and gene-therapy framework similarly emphasizes modality-specific CMC considerations, with recent guidance providing additional flexibility for CGT development while maintaining product quality and safety expectations. These developments suggest that future E&L expectations are likely to move toward a risk-based, product-specific and mechanism-informed approach.

8. CONCLUSION

Existing extractables and leachables thresholds — TTC, PDE, and AET — encode a toxicological logic calibrated for systemic, dose-proportional harm in small molecules and structurally robust biologics. This logic is necessary but demonstrably insufficient for ATMPs, whose critical quality attributes are frequently biological function, immune quiescence, and nanoscale structural integrity rather than systemic pharmacokinetic exposure alone. Ultra-low concentrations of leachables — orders of magnitude below any systemic safety threshold — can plausibly alter immune activation state, reduce transfection or transduction efficiency, compromise viral vector potency, and destabilize lipid nanoparticle assemblies through receptor-mediated, membrane-partitioning, or catalytic mechanisms that fall outside the dose-response assumptions of classical toxicology. A next-generation ATMP risk assessment framework should retain systemic toxicological thresholds where genuinely applicable, but elevate product-functional, immunomodulatory, and biophysical domains to co-primary status, anchored in product- and process-representative simulation studies, orthogonal functional bioassays, material-level QbD scoring, and modality-specific — rather than universal — thresholds. Only such a multi-domain framework can adequately protect both the patient and the therapeutic integrity of products whose very definition of "active ingredient" has outgrown the assumptions embedded in the field's founding toxicological logic.

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