

Human-Relevant Non-Animal Methodologies (NAMs)
Specialised Models Series: Renal, Dermal & Ocular
Section 6 – Reference 6.1 to 6.5

Full Scope Roadmap

6.1 Renal (Kidney) Models

6.2 Dermal (Skin) Models

6.3 Ocular (Ophthalmic) Models

6.4 Corneal Models (Standalone)

6.5 Bladder (Urological) Models

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1. Executive Summary & Legal-Scientific Imperative

The UK Animals (Scientific Procedures) Act 1986 (ASPA) imposes a statutory duty on the Secretary of State to ensure compliance with the principles of **replacement, reduction, and refinement** (the 3Rs). The statute dictates that whenever a scientifically satisfactory replacement strategy not involving protected animals is available, it must be utilised.

Historically, renal, dermal, and ocular research has relied heavily on invasive rodent and animal models, which often fail to capture complex tissue physiology and human-specific dynamic drug clearance pathways. This leads to poor predictive outcomes in clinical toxicity screenings. These translational failures occur due to:

- **Nephron and Metabolic Divergence:** Rodent kidney models often fail to replicate human glomerular filtration dynamics and drug clearance pathways, leading to poor predictive outcomes in nephrotoxicity screenings.
- **Dermal Barrier Incompatibility:** Species-specific differences in skin permeability, immune cell distribution, and lipid composition render rodent skin models non-predictive for human dermatological and cosmetic safety assessments.
- **Ocular Lacrimal and Corneal Mismatch:** Human ocular physiology is uniquely characterised by distinct tear film compositions and corneal wound-healing kinetics that are absent in common laboratory animal models, causing high rates of false-positive irritation results.

Accelerating the transition to human-relevant Non-Animal Methodologies (NAMs) is an urgent scientific necessity to bridge the translation gap and a statutory mandate for UK academic research programs under *ASPA 1986*.

To bridge this gap, this roadmap outlines a transition strategy toward human-relevant Non-Animal Methodologies (NAMs), leveraging advanced microphysiological systems (MPS) and Weight of Evidence (WoE) dossiers to support institutional Project License (PPL) applications.

2. System-Specific NAM Frameworks & Focus Areas

Focus Area	Primary Animal Model	NAM Replacement Technology	Key Scientific & Regulatory Benefit
6.1 Renal (Kidney)	Invasive rodent nephrotoxicity and cystometric models	Kidney Organoids / Nephron-on-a-chip	Overcomes rodent metabolic divergence and poor predictive drug clearance pathways.
6.2 Dermal (Skin)	In vivo skin irritation/corrosion assays	Reconstructed Human Epidermis (RHE)	Eliminates barrier incompatibility and standardises tiered toxicological safety endpoints.
6.3 Ocular (Corneal/Surface)	Animal ocular irritancy testing (Draize)	Corneal Chip architectures / TEER sensing	Bypasses non-predictive animal irritancy assays and subjective scoring.
6.5 Bladder (Urothelial)	Rodent cystometric and invasive tissue sampling	Urothelial Barrier Chip	Captures human-specific inflammatory microenvironments and multi-parametric barrier integrity.

3. Alternative Phased Implementation Timelines

Institutions can choose between a **Standard (Sequential) Roadmap** or an **Accelerated (Parallelised) Deployment Model** depending on resource allocation and project license urgency.

Option A: Standard (Sequential) Phased Implementation Roadmap

Phase & Timeline	Technological Readiness & Platform Focus	Validation Milestones	Transition & Regulatory Impact (ASPA / WoE)
Phase 1: Exploration & Audit (Months 1–6)	TRL 3–4: Assessment of legacy baseline models, bench-top circuits, and current animal-dependent assays.	* Audit current animal tissue handling workflows. * Gap analysis matching specific endpoints against human-relevant NAM alternatives.	* Establishes baseline data requirements for upcoming Weight of Evidence (WoE) dossiers. * Identifies high-priority animal replacement targets for PPL applications.
Phase 2: Pilot Integration (Months 7–18)	TRL 5–6: Integration of microphysiological systems (MPS), organ-on-a-chip platforms, and Reconstructed Human Epidermis (RHE).	* Deployment of fluidic, quantitatively driven digital platforms with automated Transepithelial Electrical Resistance (TEER) sensing. * Multi-omic barrier integrity and phenotypic characterisation.	* Bypasses non-predictive murine systemic metabolic screening. * De-risks early-stage candidate compounds before formal regulatory submission.
Phase 3: Full Qualification & Deployment (Months 19–36+)	TRL 7–9: Fully validated high-throughput organotypic systems (Renal, Dermal, Ocular, Bladder).	* Multi-organ drug clearance verification. * Cross-cutting challenge-qualification protocols completed across partner institutions.	* Direct integration into formal Home Office/ASRU project licence (PPL) applications. * Full compliance with statutory ASPA 1986 replacement duties via robust WoE dossiers.

Option B: Accelerated (Compressed) Implementation Matrix

Implementation Phase	Original Timeline	Shortened Timeline	Acceleration Strategy & Execution
Phase 1: Audit & Rapid Gap Analysis	Months 1–6	Weeks 1–4	* Utilise pre-existing template audits rather than a blank-slate review. * Focus immediately on high-priority assays (e.g., swapping standard skin irritation assays for commercial Reconstructed Human Epidermis).
Phase 2: Parallel Pilot Integration	Months 7–18	Months 2–6	* Procure plug-and-play microphysiological systems (MPS) with built-in TEER sensing instead of custom-engineering microfluidic circuits. * Run traditional animal benchmarks and NAM evaluations in parallel to fast-track confidence data.
Phase 3: Streamlined WoE & PPL Submission	Months 19–36+	Months 7–12	* Package multi-omic data incrementally into Weight of Evidence (WoE) dossiers as pilot data clears, rather than waiting for multi-organ cross-qualification to finish.

4. Systems Biology Mapping & Technical Capabilities

Bioinformatics & Multi-Omics: Integrates human-specific gene signature mapping to replace manual animal tissue histology.

Digital Pathology: Automates barrier integrity scoring and real-time sensing (TEER) for predictive toxicological modelling.

Regulatory Compliance: Directly streamlines adherence to ASPA 1986 by establishing robust Weight of Evidence (WoE) documentation for local AWERB review and Home Office/ASRU submissions.

Executive Summary & Compliance Dashboard

Executive Summary

The assessment of renal, dermal, and ocular toxicology has historically relied on high-severity *in vivo* testing, which frequently fails to replicate human-specific barrier responses. This roadmap mandates a transition to high-fidelity, human-relevant NAMs—specifically organoid and microphysiological systems (MPS)—to replace animal-based testing paradigms. This strategic shift ensures all research is scientifically precise, ethically robust, and fully compliant with the Section 2A statutory duty of the *ASPA 1986*.

Maturity Matrix

Phase 1 (Exploratory): Audit current reliance on animal-based nephrotoxicity, irritancy, and corrosion models.

Phase 2 (Pilot): Integrate human-derived organoids and barrier-on-a-chip microfluidics.

Phase 3 (Integration): Implement quantitative digital platforms for cross-cutting toxicity prediction.

Phase 4 (Standardisation): Replace 100% of high-severity animal challenge models with qualified human-relevant NAMs.

Strategic Note: Building institutional expertise in high-maturity human-relevant NAMs is essential for bridging the translational gap in these domains. By training staff in the management of complex tissue barriers and digital modelling, the institution fulfills its statutory duty under *ASPA 1986*.

Final Compliance Statement

All proposed models satisfy the Section 2A statutory duty of *ASPA 1986*. By adopting these methodologies, the institution positions itself at the forefront of the global transition toward human-centric, cruelty-free medical science.

Core Specialised Renal, Dermal & Ocular Platforms: Scientific & Regulatory Momentum

6.1 Renal / Kidney Models: Nephrotoxicity, Filtration & Regulatory Momentum

This section covers human-relevant platforms designed to model glomerular filtration barriers and tubular reabsorption. Landmark momentum in this area includes:

- **Kidney-on-a-Chip Systems:** Microfluidic devices that recreate physiological shear stress and barrier dynamics to study transporter-mediated nephrotoxicity and drug efficacy.
- **iPSC-Derived Kidney Organoids:** Three-dimensional structures that recapitulate multi-cellular nephron architecture, making them ideal for high-throughput safety screening and disease modelling.
- **Glomerular Models:** Specialised in vitro systems focused on modeling the filtration barrier and functions of the kidney's glomeruli.
- **Tubular Models:** Specialised systems designed to replicate the transport, reabsorption, and toxicity-response dynamics of renal tubules.

Artificial Intelligence (AI) and In Silico NAMs Supporting Renal Research

To complement advanced in vitro kidney models, in silico and AI-driven methodologies play a critical role in predicting safety and efficacy:

- **AlphaFold (DeepMind):** An AI system predicting protein structures, RNA, and ligand interactions to support drug discovery with far fewer molecules per program.
- **Machine Learning & AI Algorithms (e.g., QSAR):** Mathematical models used to predict chemical behaviour, real-world biological activity, and toxicity, achieving high subpopulation robustness and accuracy.

6.2 Dermal / Skin Models: Barrier Function, Toxicity & Regulatory Momentum

This section covers platforms for modelling skin barrier integrity and absorption kinetics. Landmark momentum in this area includes:

- **Reconstructed Human Epidermis (RHE):** A validated replacement model utilised for animal corrosion and skin irritation tests.
- **Full-Thickness Skin Models:** Advanced models that integrate both dermal and epidermal layers to evaluate systemic topical toxicity and permeability.

Artificial Intelligence (AI) and In Silico NAMs Supporting Dermal Research

To complement advanced in vitro skin models, in silico and AI-driven methodologies play a critical role in predicting safety and dermal absorption kinetics:

- **AlphaFold (DeepMind):** An AI system predicting protein structures, RNA, and ligand interactions to support target identification and safety assessment with far fewer molecules per program.
- **Machine Learning & AI Algorithms (e.g., QSAR):** Mathematical models used to predict chemical behaviour, skin sensitisation endpoints (such as DPRA, KeratinoSens, and h-CLAT frameworks), and toxicity, achieving high subpopulation robustness and accuracy.

6.3 Ocular / Ophthalmic Models: Irritancy, Permeability & Regulatory Momentum

This section covers models of the ocular surface and tear film. Landmark momentum in this area includes:

- **Organotypic Ocular Systems:** Advanced platforms used for quantifying drug permeability and evaluating corneal wound healing and irritancy without animal testing.
- **Ocular Microphysiological Systems:** Microfluidic models that mimic lacrimal dynamics and blood-retinal barrier (BRB) properties to evaluate ophthalmic formulations and conditions like age-related macular degeneration (AMD) and glaucoma.

- **Retinal Organoids:** Human-relevant models derived from iPSCs that confirm on-target correction of specific splicing defects and restore photoreceptor cilia function (such as for Leber Congenital Amaurosis / LCA).
- **Corneal Models (OECD-Validated):** In vitro alternatives used for chemical permeability, wound healing, and eye irritation assays as replacements for the traditional rabbit Draize test.

Artificial Intelligence (AI) and In Silico NAMs Supporting Ocular Research

To complement advanced in vitro ocular models, in silico and AI-driven methodologies play a critical role in predicting safety, toxicity, and molecular targeting:

- **AlphaFold (DeepMind):** An AI system predicting protein structures, RNA, and ligand interactions to support target identification for conditions like retinal dystrophies with far fewer molecules per program.
- **Machine Learning & AI Algorithms (e.g., QSAR):** Mathematical models used to predict chemical behaviour, real-world biological activity, and ocular toxicity endpoints with high robustness and accuracy.

6.4 Corneal Models: Safety, Wound Healing & Regulatory Momentum

This section covers specialised platforms for corneal safety assessments. Landmark momentum in this area includes:

- **Corneal-on-a-Chip Architectures:** Microfluidic devices that integrate stromal and epithelial cells to simulate the multi-layered corneal barrier and predict drug penetration and ocular toxicity.
- **OECD-Validated Corneal Equivalents:** In vitro models used for chemical permeability, wound healing, and eye irritation assays as direct human-relevant replacements for the traditional rabbit Draize test.

Artificial Intelligence (AI) and In Silico NAMs Supporting Corneal Research

To complement advanced in vitro corneal models, in silico and AI-driven methodologies play a critical role in predicting safety, molecular interactions, and ocular toxicity:

- **AlphaFold (DeepMind):** An AI system predicting protein structures, RNA, and ligand interactions to support target identification and ophthalmic drug discovery with far fewer molecules per program.
- **Machine Learning & AI Algorithms (e.g., QSAR):** Mathematical models used to predict chemical behaviour, eye irritation endpoints, and real-world biological activity with high subpopulation robustness and accuracy.

6.5 Bladder / Urological Models: Barrier Breakdown, Pathogenesis & Regulatory Momentum

This section covers platforms for modelling urothelial integrity. Landmark momentum in this area includes:

- **Urothelial Barrier-on-a-Chip:** A microfluidic platform that simulates the cyclic expansion and contraction of the bladder to study inflammatory responses and pathogen interactions in human-relevant environments.

Artificial Intelligence (AI) and In Silico NAMs Supporting Urological Research

To complement advanced in vitro bladder models, in silico and AI-driven methodologies play a critical role in predicting safety, toxicity, and pharmacological interactions:

- **AlphaFold (DeepMind):** An AI system predicting protein structures, RNA, and ligand interactions to support target identification and therapeutic development with far fewer molecules per program.
- **Machine Learning & AI Algorithms (e.g., QSAR):** Mathematical models used to predict chemical behaviour, real-world biological activity, and toxicity endpoints with high subpopulation robustness and accuracy.

These cross-cutting enabling platforms provide the multi-scale predictive power required for regulatory validation across renal, dermal, and ocular safety assessment.



Table 1: Core Specialised Platforms

Focus Area	Primary Animal Model	NAM Replacement Technology	ASPA 1986 Status
6.1 Renal	Rodent nephrotoxicity assays	Kidney Organoids / Nephron-on-a-Chip	High
6.2 Dermal	In vivo skin irritation/corrosion	Reconstructed Human Epidermis (RHE)	High
6.3 Ocular	Animal ocular irritancy testing	Organotypic Ocular Systems	High
6.4 Corneal	Animal corneal opacity/permeability	Corneal-on-a-Chip architectures	High
6.5 Bladder	Invasive rodent cystometric models	Urothelial Barrier-on-a-Chip	High

Cross-Cutting & Enabling Platforms

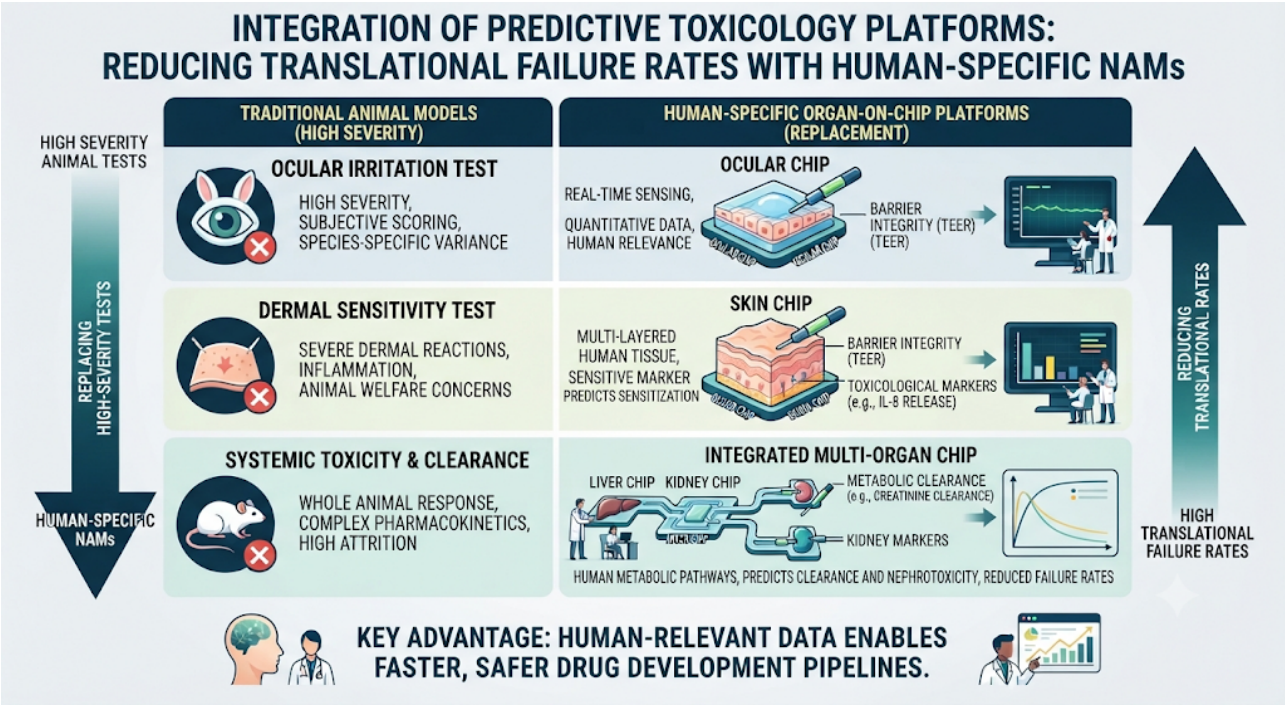


Figure 2: Integration of Predictive Toxicology Platforms

Description: A comparative matrix highlighting the reduction of "Translational Failure Rates" by deploying human-specific NAMs. It visualises how organ-specific chips provide real-time sensing of barrier integrity (TEER), metabolic clearance (renal), and toxicological markers (ocular/dermal), effectively replacing high-severity animal irritancy and toxicity tests.

Table 2: Genomic & Computational Frameworks

Platform	Key Applications	Benefits for Universities & 3Rs
Digital Pathology AI	Automated barrier integrity scoring	Replaces manual animal-tissue histology
Metabolic Pathway Sim	Predicting multi-organ drug clearance	Bypasses murine systemic metabolic screening
Systems Biology Map	Human tissue-specific gene signature mapping	Regulatory WoE for Replacement

Integration Context: Roadmap Conclusion

The modules detailed in this roadmap—from the high-fidelity renal filtration and barrier-integrity platforms explored in this section to the broader integrated cardiopulmonary and neurological frameworks established throughout this series—demonstrate that replacement is not a siloed scientific exercise, but an integrated institutional strategy. By mapping these specialised NAM-based toxicology and pathophysiology models into a unified regulatory framework, the institution moves decisively toward a standardised, human-centric research paradigm. This systemic integration is the essential prerequisite for fulfilling the ASPA 1986 statutory duty, ensuring all research is scientifically accurate, ethically aligned, and regulatory compliant.

Skills • Training, and Capacity Building

Successful adoption of high-maturity Non-Animal Methodologies (NAMs) requires a strategic shift in workforce development. To ensure the long-term success of the platforms outlined in this series, universities should prioritise the following initiatives:

Integrated Physiology & Microfluidics: Training programmes should bridge the gap between bench-top biology, fluidic circuit engineering, and complex computational mechanics.

Regulatory Competency: Staff should receive formal training on "Fit-for-Purpose" qualification and the specific regulatory expectations of the Home Office/ASRU.

Technological Literacy: Skills in microfluidic device troubleshooting, primary stem-cell differentiation, and organoid maintenance are critical for modern renal, dermal, and ocular research.

Table 3: Skills • Training & Capacity Building

Capability Domain	Focus Area	Impact on 3Rs/Replacement
Technical	Advanced MPS barrier culture & TEER sensing	Eliminates invasive animal tissue sampling
Computational	AI-driven toxicological predictive modelling	Bypasses non-predictive animal irritancy assays
Regulatory	Weight-of-Evidence (WoE) dossier creation	Streamlines compliance with ASPA 1986
Bioinformatics	Multi-omic analysis of barrier integrity	Replaces animal-based end-point toxicity studies

Clinical Translation Studies

Renal (Kidney) Models

Disease Modelling: Kidney organoids derived from human pluripotent stem cells are currently used to study inherited and acquired kidney disorders, providing insights into nephrogenesis and disease mechanisms that conventional models often miss.

Drug Screening: These platforms are increasingly applied in nephrotoxicity testing to evaluate drug-induced kidney injury, offering a more human-specific cellular context than animal models.

Translational Challenges: Despite their potential, full clinical implementation is currently constrained by hurdles such as the need for better vascularisation, long-term maturation, and scalable production.

Dermal (Skin) Models

Safety Assessment: Validated *in vitro* skin models, such as reconstructed human epidermis (RHE), are already established as alternatives to animal testing for evaluating corrosion and irritation, improving translational relevance for pharmaceutical and cosmetic safety.

Physiological Complexity: Newer biofabrication and microphysiological technologies are being developed to incorporate a greater diversity of cell types (e.g., epithelial, dendritic, and endothelial cells), which allows for more precise modelling of skin immune responses—a key area where animal models often fail to translate to human clinical outcomes.

Ocular (Eye) Models

Drug Delivery: 3D ocular organoids and "eye-on-a-chip" platforms are being integrated with advanced hydrogel-based drug delivery systems to improve the predictive capacity for ocular therapeutics.

Regenerative Potential: Research is advancing into using patient-derived cells (such as iPSC-derived retinal endothelial cells) to not only model diseases like diabetic retinopathy in a lab setting but also to potentially regenerate damaged ocular tissue *in vivo*.

Regulatory Status: NAMs, such as reconstructed human cornea-like epithelium models, are already recognised for assessing eye irritation potential for topical products.

Summary of Clinical Translational Pathway

Translational researchers are increasingly utilising these systems to recognise which preclinical advancements can be developed into new diagnostics or safety assays. However, widespread clinical adoption currently faces standardised challenges across all three areas, including the need for increased manufacturing scalability, improved characterisation, and further regulatory guidance to fully qualify these systems for broader clinical use.

Strategic Roadmap Summery

1. Vision & Mandate

Driven by the Section 2A statutory duty of the *Animals (Scientific Procedures) Act 1986*, this roadmap outlines the institutional transition from traditional *in vivo* models to high-fidelity, human-relevant NAMs. This strategy prioritises human-centric platforms to enhance scientific validity, reproducibility, and ethical alignment.

2. Landmark Regulatory & Scientific Momentum

Renal (6.1): Kidney-on-a-Chip systems recreate shear stress and tubular transport, while iPSC-derived organoids recapitulate multi-cellular nephron architecture.

Dermal (6.2): Reconstructed Human Epidermis (RHE) provides a validated, fully differentiated barrier, and full-thickness models evaluate systemic impacts of topical agents.

Ocular (6.3): Organotypic systems and ocular MPS mimic lacrimal dynamics and nutrient exchange to quantify drug permeability without animal-based irritancy testing.

Corneal (6.4): Corneal-on-a-chip architectures integrate stroma and epithelial cells to simulate the corneal barrier for accurate acute toxicity prediction.

Bladder (6.5): Urothelial Barrier-on-a-Chip simulates bladder cyclic expansion, enabling study of barrier breakdown and inflammatory response.

3. Strategic De-Risking

Financial & Temporal Efficiency: NAMs enable early-stage identification of off-target toxicities, preventing the catastrophic costs associated with late-stage clinical trial failures.

Precision Modelling: Moving away from rodent models mitigates the risk of "false positives" driven by species-specific metabolic differences that do not occur in human systems.

Data Integrity: Transitioning to human-derived data strengthens "Weight-of-Evidence" submissions, directly increasing the probability of project licence (PPL) approval by the Home Office/ASRU.

4. Compliance & Institutional Commitment

Integration Context: Mapping these specialised models into a unified regulatory framework is the essential prerequisite for fulfilling our *ASPA 1986* statutory duty, ensuring all research is scientifically accurate and ethically aligned.

Final Compliance Statement: All proposed models satisfy the Section 2A statutory duty of *ASPA 1986*. By adopting these methodologies, the institution positions itself at the forefront of the global transition toward human-centric, cruelty-free medical science.