Integrating toxicological and economic evidence to optimize repurposing strategies for rare diseases

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Background

Rare diseases present persistent challenges for therapeutic development due to small patient populations, clinical heterogeneity, and limited commercial incentives. Although biological understanding has advanced, traditional safety and efficacy development pathways remain slow and resource-intensive. Drug repurposing offers a pragmatic alternative by leveraging existing pharmacologic and toxicologic knowledge. However, most repurposing efforts prioritize biological plausibility while underutilizing structured safety and outcomes evidence. Toxicological exposure limits, organ-specific liabilities, and real-world safety signals are rarely integrated with health economic and outcomes research (HEOR) data during early candidate evaluation.

Objective

To develop and demonstrate a reproducible cross-domain evidence synthesis framework that integrates regulatory toxicology, clinical safety, mechanistic mapping, and translational/economic signals to inform rare disease repurposing decisions.

This framework was applied to evaluate the feasibility of extending **pirfenidone from its approved idiopathic pulmonary fibrosis (IPF) indication to systemic sclerosis–associated interstitial lung disease (SSc-ILD)**.

Case study rationale

Pirfenidone, approved for **IPF**, was selected for evaluation in **SSc-ILD** because:

- Its chronic exposure margins and regulatory toxicology profile are established in IPF, enabling cross-species NOAEL comparison and exposure normalization.
- IPF and SSc-ILD share overlapping profibrotic signaling pathways, including TGF-β and PDGF networks.
- SSc-ILD represents a high-morbidity rare disease with persistent unmet need.
- The translational landscape remains fragmented, providing a model for structured integration of multi-domain evidence.

Integrated cross-domain evidence framework

Four structured biomedical data sources were integrated:

1	**PharmaPendium** Reg tox • NOAEL AUC/Cmax, chronic tox	**Embase** Trials + PV Emtree → SOC AEs	**Embiology** Targets / pathways Ontology mapping	**Scopus** Topic clusters Networks, maturity
2	**Harmonize and Normalize** Cross-species exposure normalization (AUC/Cmax) • MedDRA organ mapping • Emtree SOC aggregation • Pathway ontology alignment • Bibliometric clustering metrics			
3	Safety window Exposure thresholds + liabilities	**Safety concordance** Clinical trials + PV SOC patterns	**Plausibility** Pathway convergence	Burden / Readiness Monitoring burden + maturity
4	**Qualitative Integration Matrix → Decision Support** Outputs: GO / Conditional / Data Gap • Dose feasibility hypotheses • Monitoring considerations • Evidence gaps for follow-up studies			

Evidence sources and standardization

- **PharmaPendium:** NOAEL extraction; cross-species exposure normalization (AUC/Cmax); MeDRA organ mapping.
- **Embase:** Emtree harmonization; SOC-level aggregation across trials and post-marketing safety.
- **Embiology:** Target identification and pathway ontology mapping of fibrotic signaling.
- **Scopus:** Bibliometric clustering and collaboration network analysis to assess translational maturity.
- **Integration:** Terminology alignment and exposure normalization enabled construction of a qualitative cross-domain decision matrix.

Pirfenidone safety concordance across evidence streams (Embase; IPF anchor)

Qualitative SOC-level synthesis based on Embase-indexed trials, pooled analyses, post-marketing surveillance, and real-world observational studies (Emtree harmonization).

System Organ Class (SOC)	Clinical trials / pooled analyses	Post-marketing surveillance & PV	Real-world / observational	Example events (PT-level examples)
Gastrointestinal disorders	✓	✓	✓	Nausea; diarrhea; dyspepsia
Skin & subcutaneous tissue disorders	✓	✓	✓	Photosensitivity; rash
Hepatobiliary disorders	✓	✓	✓	ALT/AST elevations; LFT monitoring
Nervous system disorders	✓	✓	✓	Dizziness; headache
General disorders	✓	✓	✓	Fatigue
Treatment discontinuation (tolerability)	—	✓	✓	Dose interruption; discontinuation (subset)

Legend: ✓ = reported across evidence streams; — = not assessed / stream-specific

Representative Embase-indexed sources: Trial efficacy/safety [1]; pooled safety analysis [9]; post-marketing surveillance [13]; real-world observational studies [8,11,14,15]; pharmacovigilance database analysis [16]; safety management review [19].

Pirfenidone safety concordance across evidence streams (Embase; IPF anchor)

Embase-indexed trials, pooled analyses, post-marketing surveillance/pharmacovigilance, and real-world observational studies were harmonized at the system organ class (SOC) level using Emtree indexing to enable cross-stream comparison. Reported safety domains were consistent across evidence streams, with gastrointestinal, skin/photosensitivity, hepatobiliary (LFT elevations), nervous system (dizziness/headache), and general disorders (fatigue) signals recurring across controlled and real-world settings.

Scientific rationale for case study selection*

Selection Criterion	Scientific basis	Elsevier data source & analytical function	Alignment in Pirfenidone-SSC-ILD
Regulatory safety & exposure definition	Requires cross-species NOAEL characterization, exposure normalization (AUC/Cmax), and identification of chronic dose-limiting toxicities.	**PharmaPendium:** Regulatory toxicology extraction; NOAEL and exposure harmonization; MEDRA-aligned organ toxicity mapping; cross-species threshold comparison.	Defined chronic exposure margins and organ-specific liabilities.
Clinical safety reproducibility	Requires standardized SOC-level aggregation across trials and pharmacovigilance sources.	**Embase:** Entree-controlled vocabulary harmonization; integration of clinical and post-marketing adverse event data; longitudinal safety synthesis.	Consistent adverse event patterns relevant to chronic antifibrotic therapy.
Mechanistic convergence	Requires target-level and pathway-level mapping across fibrotic signaling networks.	**Embiology:** Structured molecular target identification; pathway ontology integration; assessment of TGF-β and PDGF signaling overlap.	Demonstrated convergence with SSC-ILD profibrotic pathways.
Rare disease burden & unmet need	Requires characterization of disease severity, progression, and therapeutic constraints.	**Embase & Scopus:** Clinical phenotype literature synthesis; epidemiologic density assessment; therapeutic landscape mapping.	High-morbidity ILD phenotype with limited alternatives.
Translational evidence maturity	Requires bibliometric evaluation of research density and collaboration structure.	**Scopus:** Topic clustering; co-authorship network analysis; translational landscape fragmentation assessment.	Active but non-consolidated research ecosystem.

*Case study selection was informed by structured cross-domain evidence integration across regulatory, clinical, mechanistic, and translational datasets

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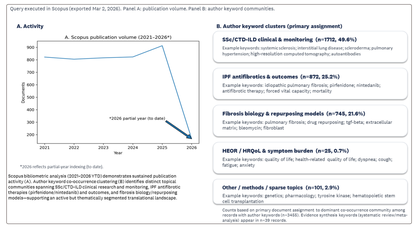
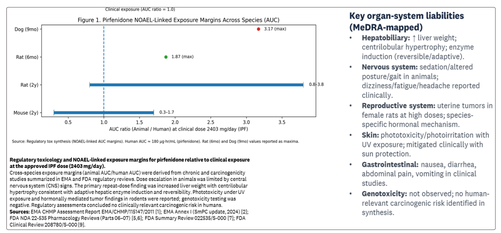
*references used in study also available upon requests

Scopus translational landscape: Activity and thematic segmentation



Pirfenidone regulatory toxicology summary (IPF anchor)

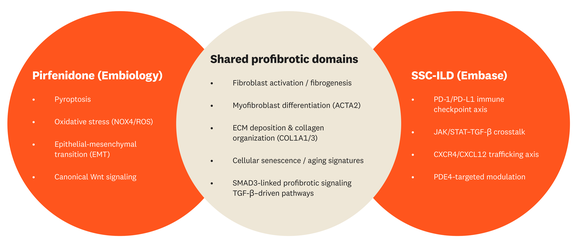


Key organ-system liabilities (MeDRA-mapped)

- **Hepatobiliary:** ↑ liver weight; centrilobular hypertrophy; enzyme induction (reversible/adaptive).
- **Nervous system:** sedation/altered posture/gait in animals; dizziness/fatigue/headache reported clinically.
- **Reproductive system:** uterine tumors in female rats at high doses; species-specific hormonal mechanism.
- **Skin:** phototoxicity/photoirritation with UV exposure; mitigated clinically with sun protection.
- **Gastrointestinal:** nausea, diarrhea, abdominal pain, vomiting in clinical studies.
- **Genotoxicity:** not observed; no human-relevant carcinogenic risk identified in synthesis.

Mechanistic domain domain overlap for pirfenidone repurposing

Ontology-level mapping of pirfenidone-associated processes (Embiology export) against SSC-ILD fibrosis pathway domains (Embase evidence)



Mechanistic domain overlap for pirfenidone repurposing (Embiology and Embase)

Pirfenidone-associated processes (Embiology) were extracted from Embiology and summarized at the pathway/process domain level (export date: 03 Mar 2026). SSC-ILD fibrosis pathway domains were derived from Embase-indexed mechanistic literature. Overlap highlights convergent profibrotic domains, including fibroblast activation, ECM programs, senescence, and SMAD3-linked signaling, consistent with TGF-β–driven fibrotic pathways.

Conclusion

Reproducible framework supports evidence extension to a rare fibrotic disease, integrating toxicology, safety, mechanistic, and HEOR data to enable structured, transparent repurposing decisions.

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