REGULATORY INNOVATION

ScieGen Pharmaceuticals Inc.

PHARMA REACH LLC

Expanding AI & ML in Generic Drug Submissions

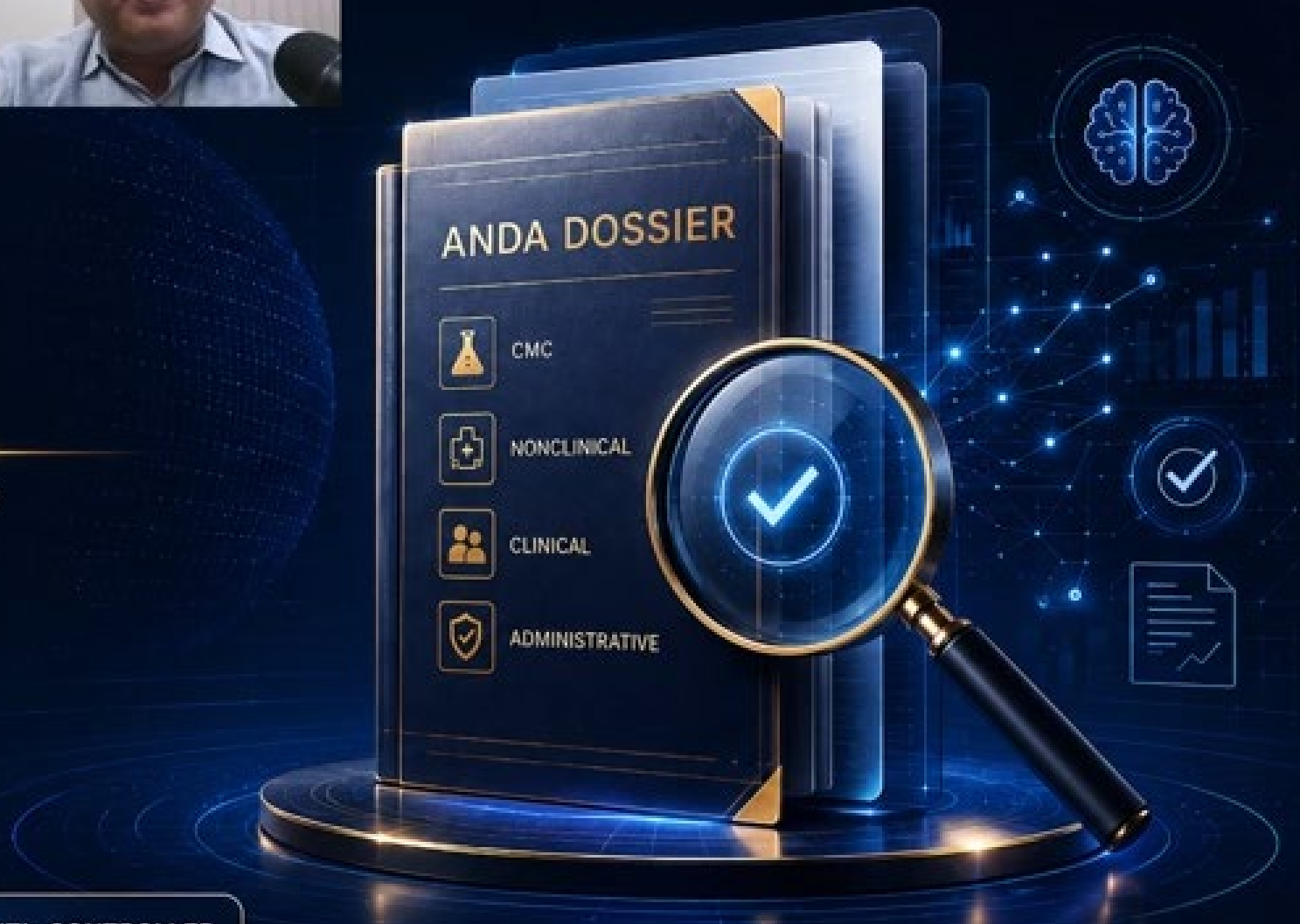
Integrating LLM-Based Pre-Submission Audits to Mitigate First-Cycle ANDA Deficiencies

Presented by

Raghu Ram Pannala, Ph.D.

ScieGen Pharmaceuticals Inc.

Supported by Pharma Reach LLC



FY 2026 GDUFA Workshop

FDA-ALIGNED | CMC-FOCUSED | HITL-CONTROLLED

REGULATORY INNOVATION

ScieGen Pharmaceuticals Inc.

PHARMA REACH LLC

First-Cycle Review Readiness Challenge

Why do many ANDAs receive deficiencies during initial review?

1

Review Readiness

Submission-quality risks remain unresolved

2

CMC, BE, and Dossier Alignment Gaps

3

IRs, DRLs, CRLs

Can delay market entry

4

Early Detection Opportunity

Improve review readiness before FDA submission

> *"Early detection of submission-quality risks can improve review readiness."*

FY 2026 GDUFA WORKSHOP

Raghu Ram Pannala, Ph.D. • ScieGen Pharmaceuticals Inc.

Module 3 vs. Module 2.3 Alignment Gaps

Manual dossier assembly creates compounding risks across the submission lifecycle.

MODULE 3
Quality / CMC

Alignment risk zone

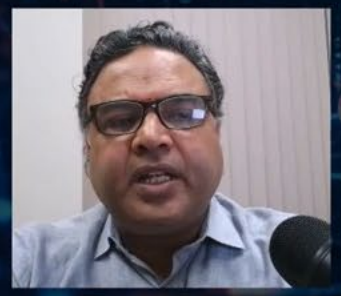
MODULE 2.3
Quality Overall Summary

ROOT CAUSES

- Transcription and omission errors
- Data drift across revisions
- Inconsistent cross-references

COMMON TRIGGER POINTS

- Batch numbers
- Specifications and analytical limits
- Manufacturing controls
- Impurity controls and nitrosamine risk assessments
- Process validation
- Stability commitments
- BE study design alignment



> “Unresolved gaps may become IRs, DRLs, or CRLs.”

REGULATORY INNOVATION

ScieGen Pharmaceuticals Inc.

PHARMA REACH LLC

Automated Digital Audits

Multi-agent RAG architecture for pre-submission review readiness.

FDA-ALIGNED DIRECTION

AI-supported pre-submission audits strengthen review readiness and support human regulatory judgment.

FY 2026 Alignment

Directly supports CDER AI/ML expansion priorities and GDUFA science initiatives

ANDA Dossier → Source Retrieval → Agentic Comparison → HITL Disposition → Audit Report

PURPOSE

Strengthen regulatory judgment by identifying inconsistencies earlier and organizing them into traceable, evidence-based audit outputs.

IT CONTROLS

- Source retrieval controls
- Version control and audit logging
- Prompt governance
- Human review before acceptance

Case-study validation: after HITL review and temporal calibration, retained AI findings matched actual FDA deficiencies in the evaluated examples.

REGULATORY
INNOVATION

ScieGen Pharmaceuticals Inc. | PHARMA REACH LLC

Explainability by Design

FDA-aligned 7-step credibility framework with ontology-free design and end-to-end traceability.

1. Question of Interest
2. Context of Use (COU)
3. AI Model Risk
4. Credibility Plan
5. Execute Plan
6. Document Results & Deviations
7. Determine Adequacy for COU

Ontology-Free Design Retained
Source-grounded retrieval and extraction without dependence on a fixed ontology.

Full Traceability Retained
Module section, QOS statement, study document, supporting passage, rationale, and reviewer disposition remain visible end-to-end.

> Explainability requires both FDA-aligned credibility assessment and citation-linked traceability.

Reference: FDA draft guidance on AI to support regulatory decision-making describes a 7-step risk-based credibility assessment framework for a specific context of use.

Raghu Ram Pannala, Ph.D. • ScieGen Pharmaceuticals Inc.

REGULATORY INNOVATION

ScieGen Pharmaceuticals Inc.

PHARMA REACH LLC

Three-Phase Pipeline

From specialized audit agents through eCTD readiness and continuous optimization.

01 Specialized Agent Deployment

- **Direct Matcher:** exact text, table, and numerical comparisons
- **Transitive Linkage Agent:** cross-module semantic linkage
- **PSG Compliance Agent:** product-specific BE and PSG alignment review

02 eCTD 4.0 Readiness

- Future-ready submission architecture
- Context-of-use tags and structured metadata
- Document lifecycle tracking

03 Continuous Prompt Optimization

- Sponsor-specific calibration and audit logs
- Version-controlled prompts and guardrails
- False-positive reduction with HITL validation

Learning audit framework: precision improves over repeated submission cycles.

A states CDER and CBER accept new regulatory applications in eCTD v4.0 format beginning September 16, 2024.

REGULATORY INNOVATION

Pre-Submission Audit: Model Audit Report

Evidence-linked pre-submission readiness output.

ScieGen Pharmaceuticals Inc.

PHARMA REACH LLC

Finding ID
Unique identifier for each audit finding.

Module / Section
Precise location within the eCTD.

Source Citation
Direct link to the source document and location.

Risk Category
Regulatory significance classification.

[redacted]

Audit #	AUDIT-#667-FDA-GDFA-FY26-Model - ScieGen CDAR (BioPharm/Nonclinical)
SOP	SCG-2022
Date	May 5, 2025 (v1.0)
Audit Type	Pre-Meet Only Submission Package - Type B (React. & Primary Biological Mode - BNo/DMF)
Your Submission:	NDA 123456
SEVERITY LEGEND:	RTI (Trackable) / MAJOR (1/2) / MINOR (3) / No RTS

EXECUTIVE SUMMARY

Applied Pre-FDA GDFA 2027 Submission Compliance standards (ICH M4Q, ICH M3, ICH M4S, ICH E2C/D/Q/F, SBA). This audit identified 14 Total Findings – 2 RTI, 8 Major, 3 Minor, 1 No RTS. All findings include direct traceability to source documents in eCTD (table below) with evidence linkage, risk-based classification, and recommended remediation.

Key Findings at a Glance

ID	Module / Location	Finding Summary	Severity
DF-194	M4 / 2.3.2	Stability protocol missing ±5 °C accuracy with continuous probe (P.8.4–100).	Major R2
DF-310	M3 / 1.2.1	CDS backbone validation: final sequence breaks.	Minor R3
DF-415	M5 / 5.3.1.2	AE method table inconsistent in Risk (TOC/outcome vs. editorial).	Major R2
DF-906	M5 / 5.3.1.1.2	CSR is red OCE is in table 25-2.1 PBR portion (unexpected ERF)	Major R2
DF-816	M5 / 5.1.1.2	Nonclinical 4.2.1.2 inconsistencies in NMR QC (9.2.1.4).	RTI Trigger

ID	Module / Location	Finding Summary	Severity
DF-194	M4 / 2.3.2	Non-clin overview does not align to proposed label.	Major R2
DF-310	M3 / 1.2.1	CCD backbone validation: final sequence breaks.	Minor R3
DF-415	M5 / 5.3.1.1.2	AE method table inconsistent in Risk (TOC/outcome vs. editorial).	Major R2
DF-906	M5 / 5.3.1.1.2	CSR is red OCE is in table 25-2.1 PBR portion (unexpected ERF)	Major R2

[redacted]

[redacted]

ANDA Approved in 11 months

AI Rationale
Explainable reasoning with regulatory basis.

Human Reviewer Decision
Expert judgment with accountability.

Disposition: Retain / Omit / Monitor
Final readiness disposition.

Traceable
Every finding is linked to source evidence.

Defensible
AI rationale + human oversight = credibility.

Actionable
Clear dispositions drive targeted remediation.

Audit-Ready
Structured output aligned with FDA expectations.

Time-Saving
Faster reviews, fewer cycles, higher quality.

A structured, traceable audit trail before ANDA submission.

Raghu Ram Pannala, Ph.D. • ScieGen Pharmaceuticals Inc.

CASE STUDY 1

Product A DR Tablets — Audit Findings Flow

Initial sensitivity followed by HITL + temporal filtering.

20 potential issues initially flagged → **15** omitted as artifacts → **5** true deficiencies retained

OMITTED RESULTS — REASON

- Legacy or contextual artifacts
- Expired batch references
- Outdated stability timepoints
- Historical information that no longer reflects current submission context

VALIDATION OUTCOME

Five retained deficiencies matched actual FDA findings in the case-study comparison.

AI provided high sensitivity; HITL review provided regulatory precision.

CASE STUDY 2 — BEFORE OPTIMIZATION

Product B — Immediate-Release Tablets

Three-year-old application · Modules 1, 2, 3.2.S, 3.2.P, and 5

8
findings initially flagged
3 major · 5 minor

→ **Temporal context not fully calibrated** →

Over-review of historical information

OMITTED RESULTS — REASON

- Historical batch expiry dates
- Outdated stability references
- Legacy module context
- Findings not relevant to the current submission state

KEY LEARNING

Legacy applications require timeline-aware prompt logic and human regulatory review before findings are accepted.

CASE STUDY 2 — AFTER OPTIMIZATION

Product B — Results & Validation

Prompt refinement + application timeline calibration.

8
before optimization findings flagged

→ **Temporal Calibration** →

3
true deficiencies retained

OMITTED RESULTS

False-positive temporal artifacts removed after prompt refinement and application timeline calibration.

VALIDATION OUTCOME

All three retained findings matched actual FDA findings in the case-study comparison.

100% match for retained case-study findings — not a claim of universal model accuracy.

HUMAN IN THE LOOP

Fine-Tuning & Oversight

> “Human-in-the-loop oversight is the control layer that makes AI usable in regulatory science.”

The True Value of AI

Rapid, sensitive detection of potential dossier risks.

Iterative Teaching Required

Product-specific, site-specific, and timeline-specific calibration.

Human Oversight Is Essential

Experts validate findings, disposition omissions, and ensure scientific and compliance accuracy.

AI brings speed and sensitivity. Human expertise brings judgment, accountability, and regulatory meaning.

FY 2027 Roadmap / Proposed Next Steps

ScieGen Pharmaceuticals Inc. | PHARMA REACH LLC

Roadmap for AI-supported, human-validated pre-submission audit deployment.

01 Strategic Alignment

Advance multi-agent RAG architecture as a formal pilot framework aligned with FY 2027 CDUFA science initiatives and CDER priorities.

02 Iterative Pilot Programs

Evaluate the digital audit tool across legacy and new ANDA submissions to improve product-specific calibration, review readiness, and operational learning.

03 Establish Industry Standards

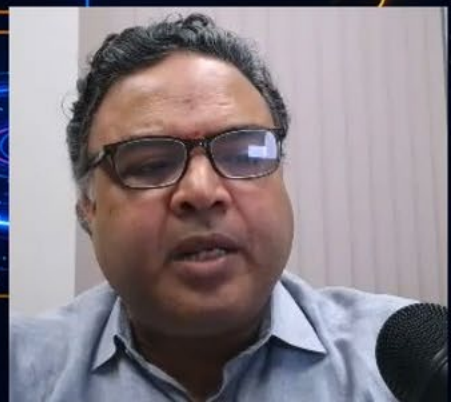
Develop HITL validation, audit-trail, prompt-governance, and source-citation standards through cross-functional collaboration.

Toward fewer first-cycle deficiencies through AI-supported, human-validated pre-submission audits

A practical path to stronger review readiness, better traceability, and higher submission quality.

Thank You

Special Thanks to ScieGen Pharmaceuticals Inc., Management
[Dr. Pailla Malla Reddy, Pailla Saketh Reddy and Palempalli Siva Reddy]
RA Team & Pharma Reach LLC, Sri Mukkamala



Raghu Ram Pannala, Ph.D. • ScieGen Pharmaceuticals Inc. • Pharma Reach LLC • FY 2026 GDUFA Workshop