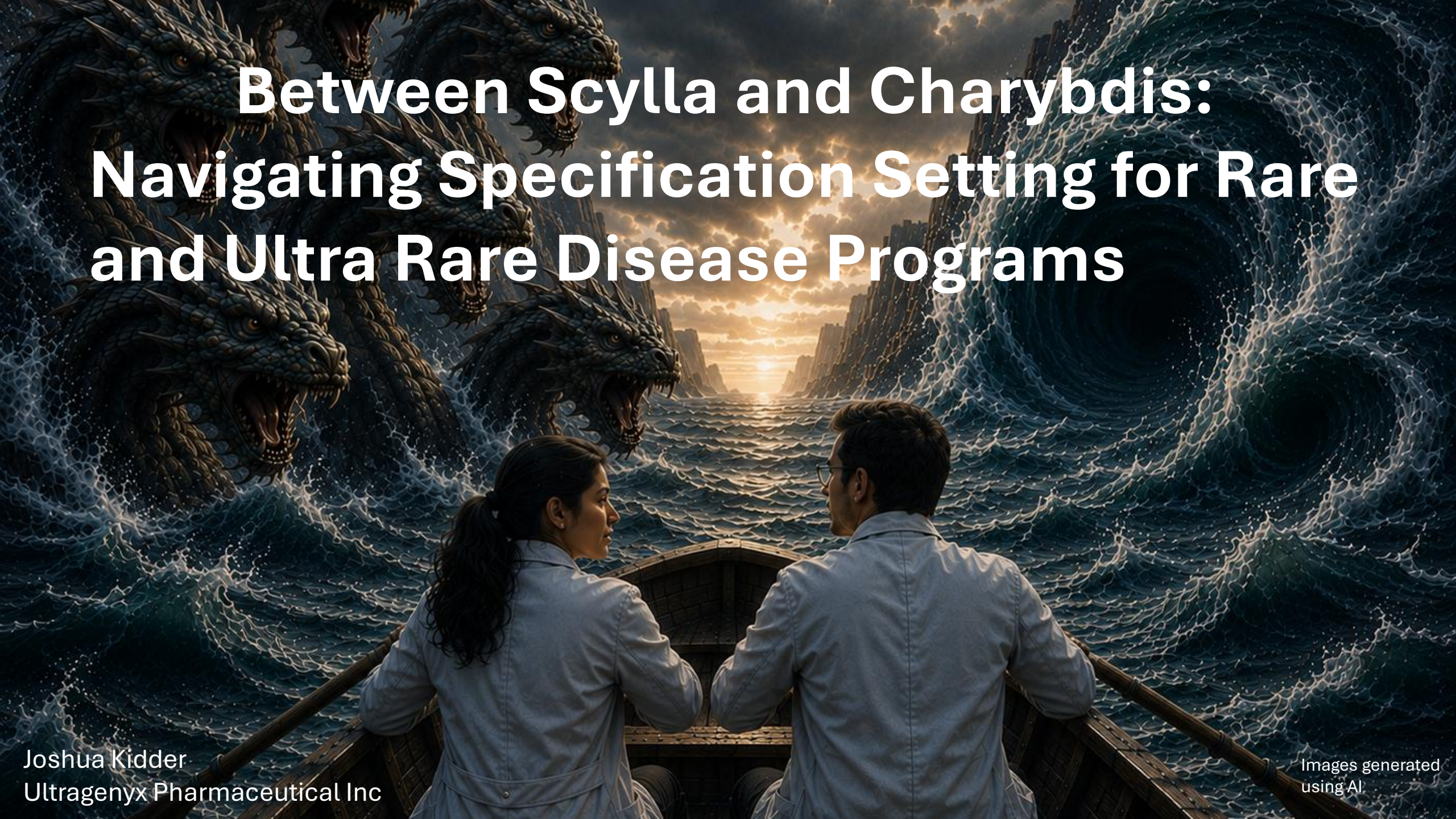
Between Scylla and Charybdis: Navigating Specification Setting for Rare and Ultra Rare Disease Programs



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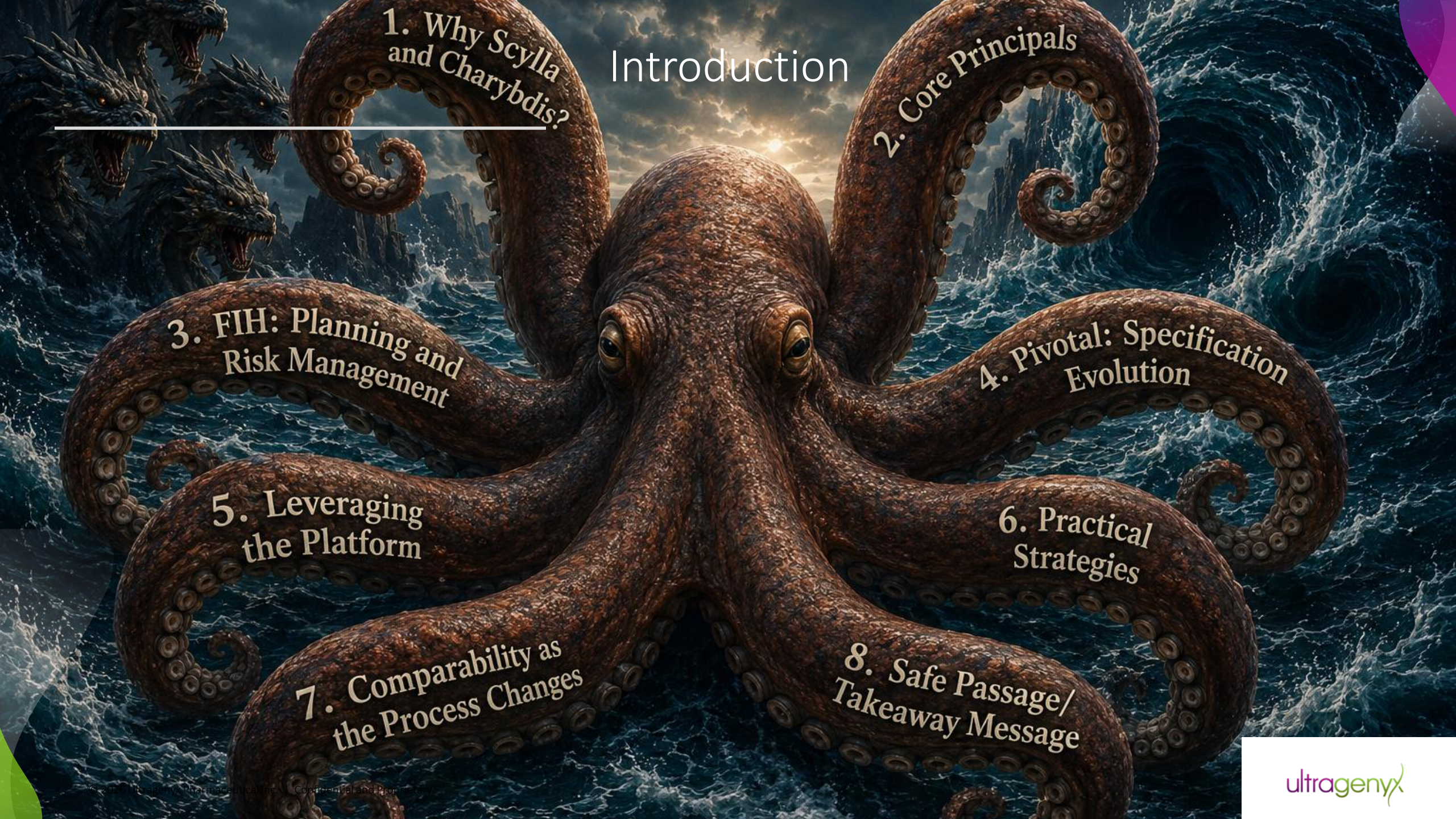
Introduction



Why Scylla and Charybdis?

- The story
- ICH Q9 principals exists even in ancient times →certainty vs. consequence
- How is this relevant to specification setting?

Overly Permissive (Scylla)	Risk/Consideration	Overly Restrictive (Charybdis)
X	Material suitable for FIH but not Pivotal	
	Material not suitable for FIH or Pivotal	X
	Relaxing a specification is more of a regulatory challenge than tightening a specification	X
	Limited ability to refine at stage gates (ex. ahead of pivotal trial)	X

Core Principles

FIH: Planning and Risk Management

Early phase limits are intentionally more permissive and based on risk acceptance

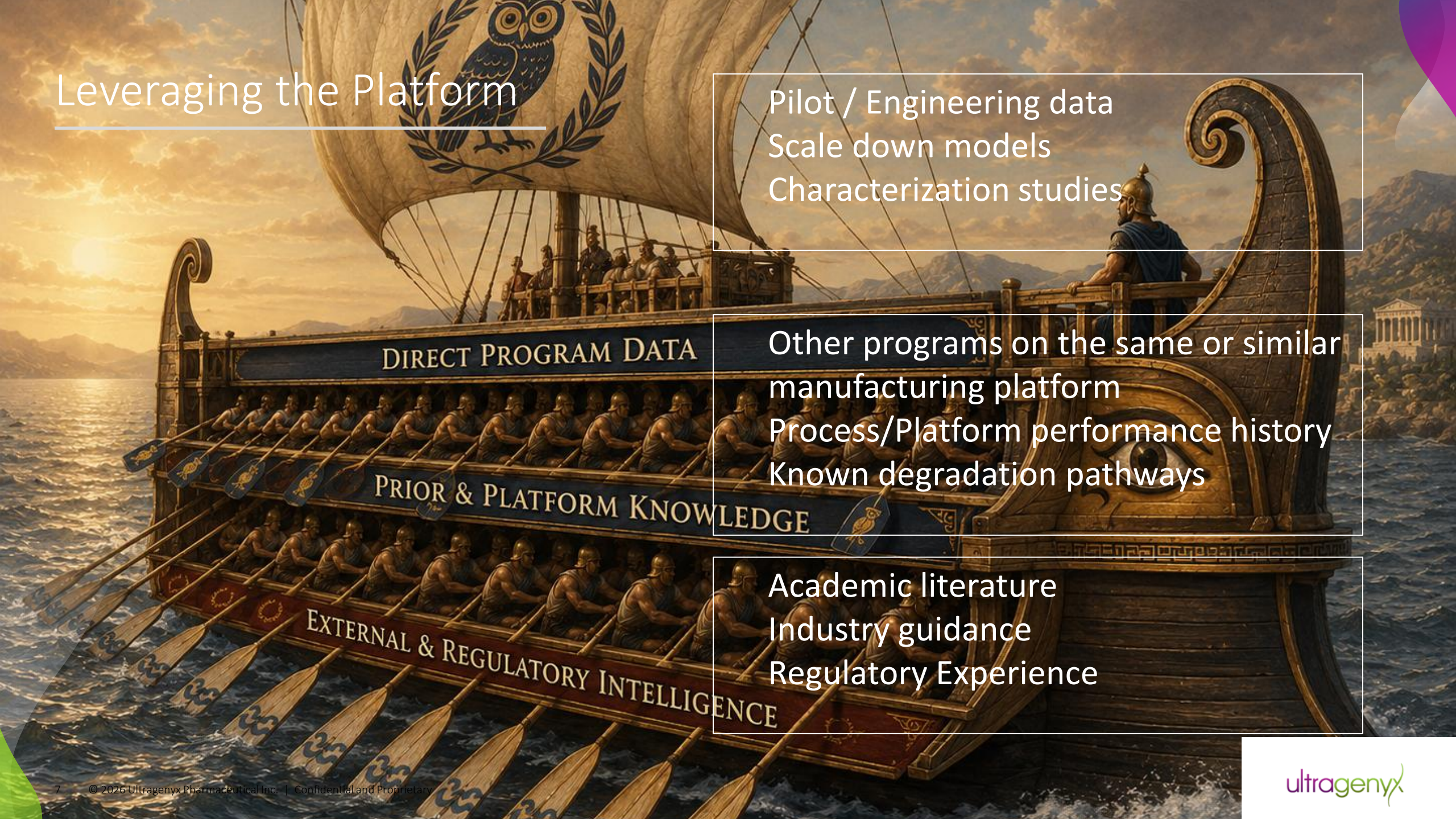
- Declare intent. Specification reassessment at stage gates (ex. before Pivotal trial)
  - What will be reassessed?
    - Characterization methods moved to release test panel or discontinued not maintained for perpetuity.
    - Assess process & method capability. Determine is existing limits remain appropriate or should they evolve
- Criticality navigates
  - CQAs may need tighter limits or a more robust justification than a non CQA
  - Not all attributes require the same level of rigor
- "Report Results"?
  - CQA vs. pCQA/non-CQA
  - If you expect that is may matter later, control now if broadly.

Pivotal: Specification Evolution

This is a stage gate—reassess limits ahead of Pivotal trial

- Method Maturity
  - Validation for all analytical methods
- Process understanding-What has been learned?
  - Characterization studies (ex. hold time)
  - Pilot or ENG runs?
- Report Results→ numeric limits
  - This is a temporary state, not a long-term control strategy

Leveraging the Platform



Pilot / Engineering data
Scale down models
Characterization studies

Other programs on the same or similar manufacturing platform
Process/Platform performance history
Known degradation pathways

Academic literature
Industry guidance
Regulatory Experience

Practical Strategies

Attribute	Method	FIH	Pivotal
General	pH, Osmo, etc.	Numeric results	Numeric results
Safety	Bioburden & etc.	Per compendia	Per compendia
Identity	ID #1 and ID #2	Meets Identity criterion	Meets Identity criterion
Concentration	Vector	Numeric range	Nominal ± 15%
	Particle	Report Results	Numeric range
Potency	$TCID_{50}$	Report Results	N/A
	Expression	50 - 150%	70 - 130%
	Functional	N/A	50 - 150%

Practical Strategies

Attribute	Method	FIH	Pivotal
Purity and Impurities	CE-SDS	>90%	>95%
	%Aggregation	Report Results	Numeric limit
	DNA impurity #1 (CQA)	Numeric limit	Numeric limit
	DNA impurity #2 (pCQA) #3 (non CQA)	Report Results	N/A
	HCP	Report Results	Numeric limit
	Affinity Ligand	Report Results	N/A
	Capsid Composition	Report Results (%Full, %Empty)	Numeric Range

Comparability Considerations

Manufacturing process may change from FIH to Pivotal

- Regulatory expectation that Comparability is evaluated
- Limited data posed a challenge for specification setting and this carries over to comparability
- Challenges to consider:
  - Limited pre-change data set
  - Limited post-change data set
  - Setting Comparability acceptance criteria (often tighter than specification)
  - Material availability
  - Method availability

Safe Passage (Conclusion)

Our responsibility is not to imagine certainty exists where it does not but rather to navigate deliberately and safely

- Start broad but not blind
  - Broad doesn't mean arbitrary, it means justified and with a plan

- Let risk severity guide
- Plan intentionally for specification evolution through state gates and as understanding progresses
- Sound scientific judgement must remain at the helm