# Shoring up Your Platform: Applying Knowledge Management and Regulatory Considerations to Gene Therapy Development

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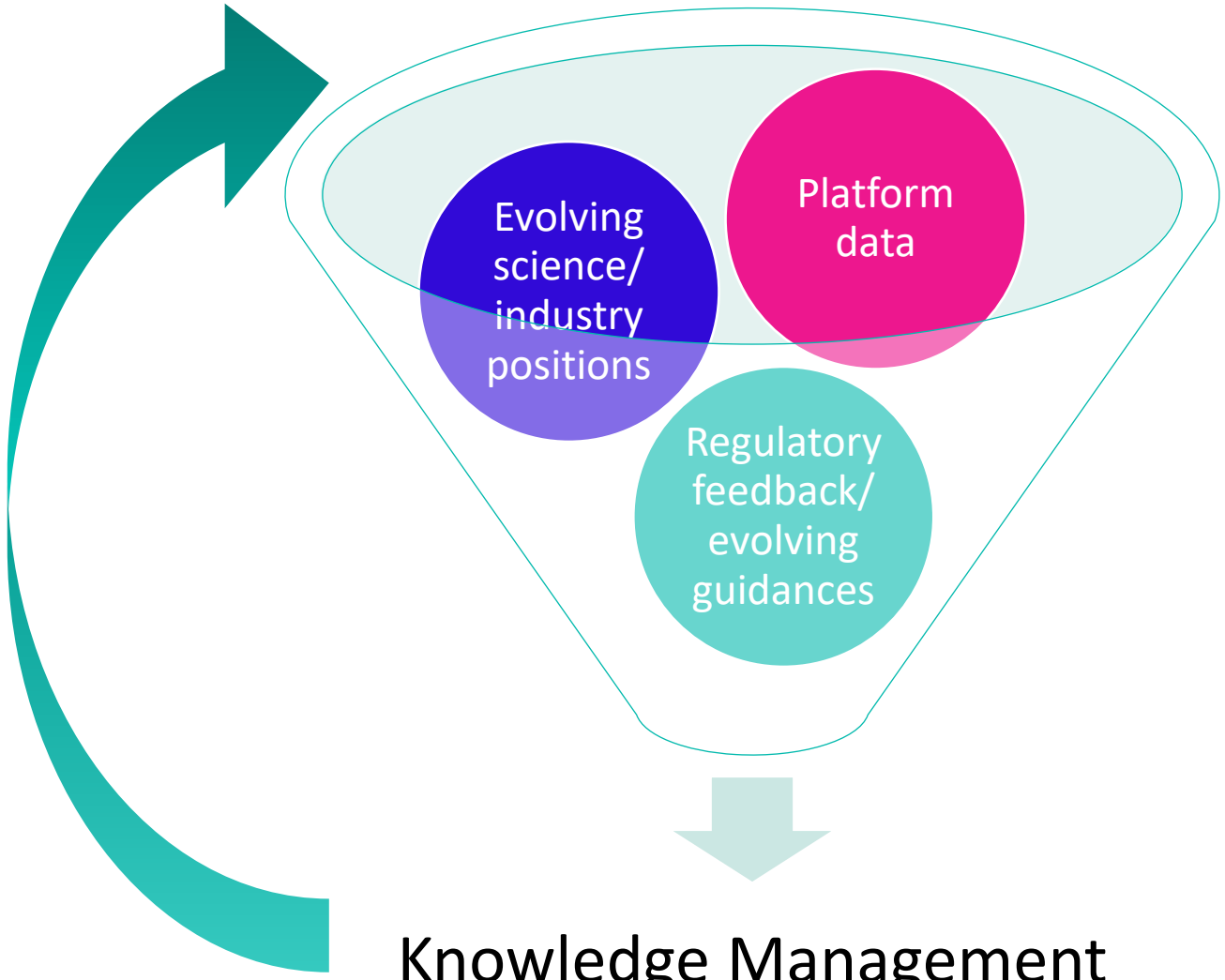
# Outline

- Platform approaches and knowledge management
- Overview of Ultragenyx gene therapy pipeline
- Pinnacle manufacturing platform and regulatory feedback
- Platform control strategies and regulatory feedback:
  - Specification setting and justifications
  - Removal of infectious titer by $TCID_{50}$ testing
  - Bioburden testing
  - Capsid testing and characterization
- Conclusions and recommendations

# Platform Approaches

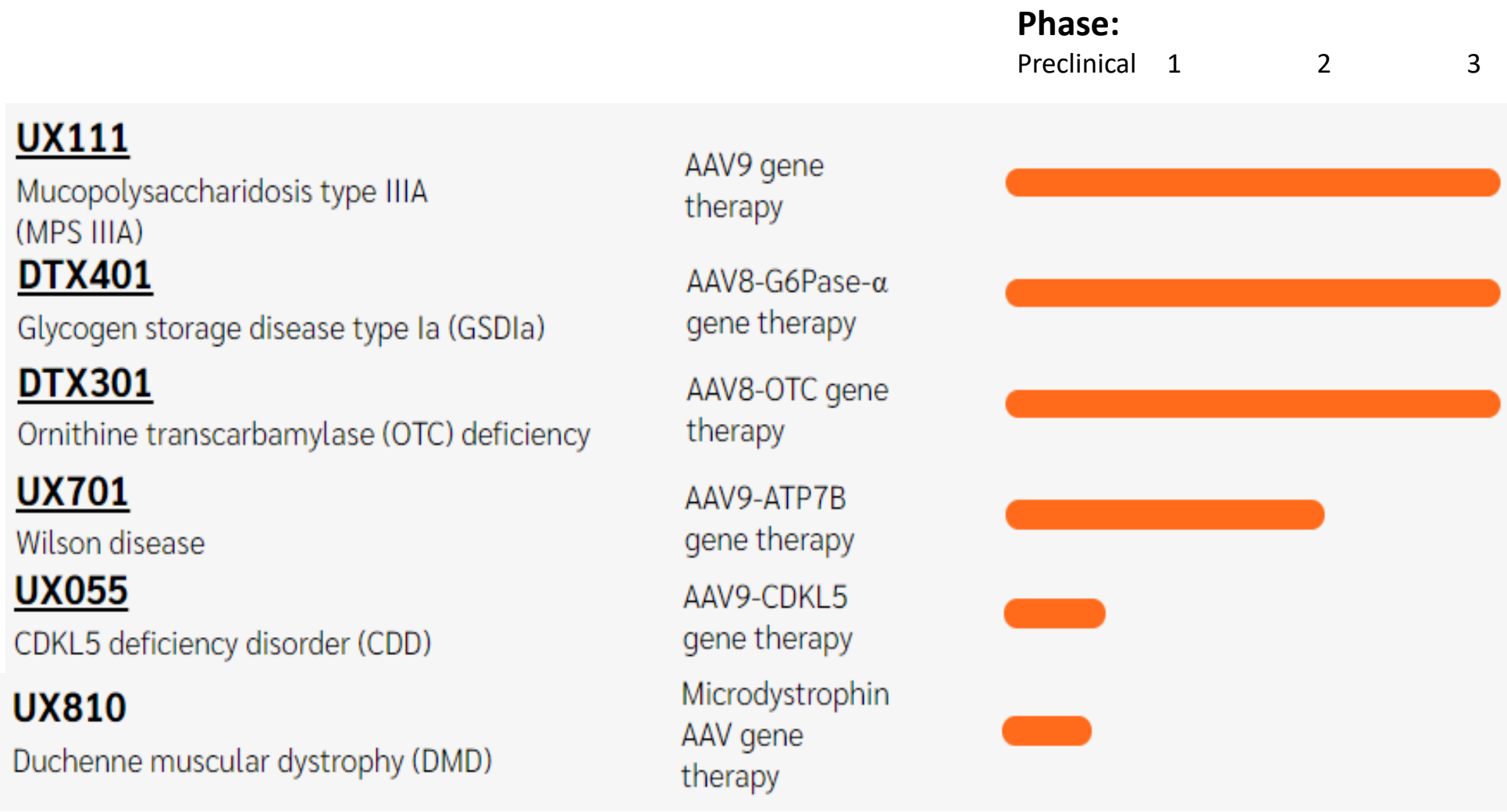
- “Platform” can apply to multiple aspects:
  - Manufacturing process
  - Facility design
  - Control strategy
  - Phase-appropriate strategies
  - Method development
- Company positions or platforms are subject to change with additional knowledge and data
  - This can include regulatory feedback and evolving guidances
  - New data and industry position papers can help inform platform positions

# Relationship Between Platform Approaches and Knowledge Management



# Gene Therapy Pipeline and Pinnacle PCL™ Platform

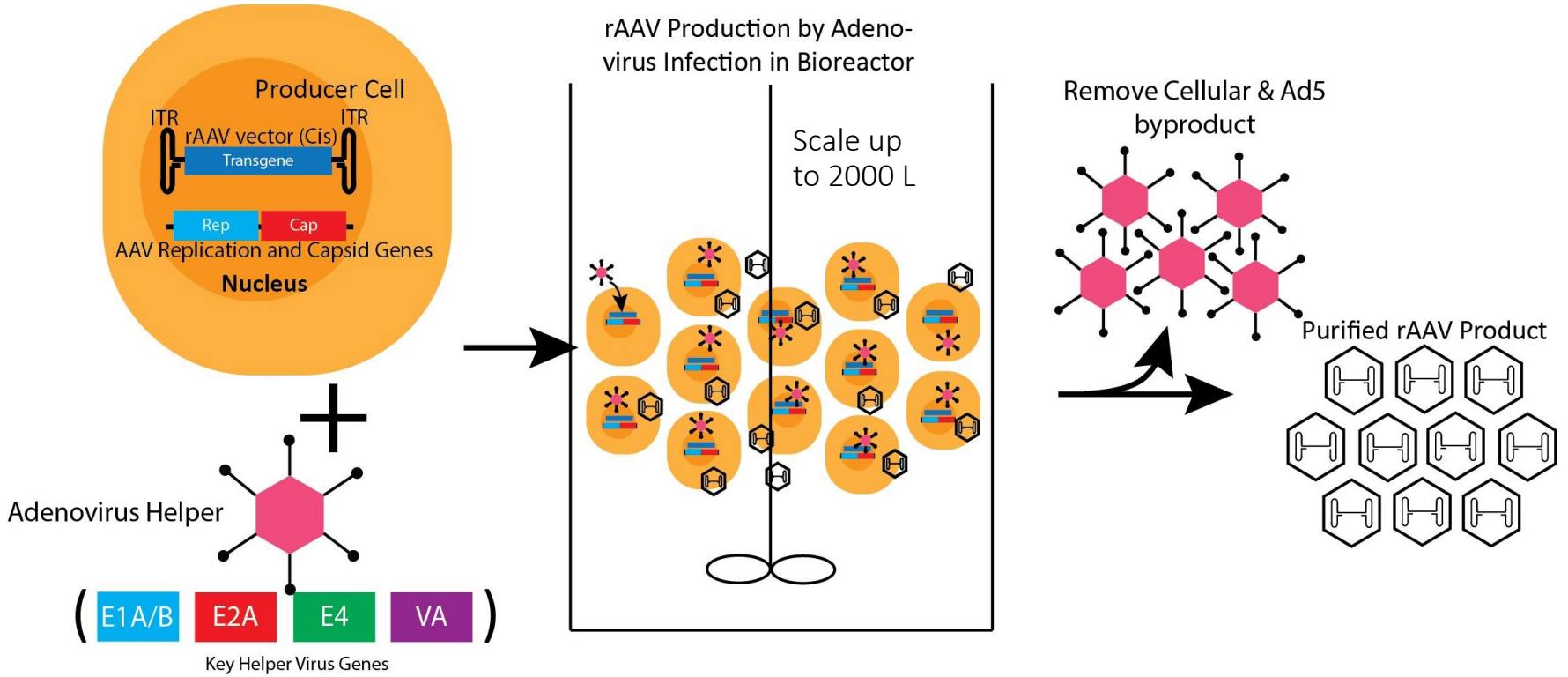
# Introduction – Ultragenyx Gene Therapy Pipeline



# Pinnacle PCL™ Manufacturing Platform

- Efficient and scalable production of AAV gene therapies
- Utilizes Producer Cell Line (PCL) technology, which allows for production of high yields of adeno-associated virus (AAV) vectors, while maximizing the production of full AAV capsids
  - Serum-free suspension culture
  - Process involves infection with a helper virus (Ad5)
  - Reproducibly scalable to 2000 L
  - Maintains AAV production at high volumetric productivity
  - Cost of goods reduced compared to transfection-based AAV platforms
  - Process is easily transferrable

# Overview of the Pinnacle PCL™ Platform 2000 L Batch Process







Figures courtesy of Ultragenyx Pharmaceutical Development

# What's Important to Understand from Pinnacle Process Re: Platform Regulatory Approaches?

- The Pinnacle PCL™ platform has been utilized to manufacture several gene therapy AAV products in various stages of clinical development (Pre-IND through Phase 3)
  - Able to obtain commercial-ready scale process at Pre-IND stage based on platform data from later stage programs
  - Global clinical trial applications reference platform data for various attributes
- Expected process-related and product-related impurities:
  - Host-cell protein
  - Residual Rep and Cap DNA
  - Residual host-cell DNA (PCL-related)
  - Ad5-related impurities
  - Benzonase
  - Affinity ligand
  - Empty/partial capsids
- Knowledge management – we can use data across products to help understand:
  - Key process steps and their capabilities in terms of impurity and viral clearance
  - Acceptable limits for critical quality attributes
  - Stability-indicating attributes

# Key Lessons Learned from Regulatory Feedback on use of Pinnacle Platform:

- In the early days….everything was “report results”
  - BUT….we wanted to use platform data for aspects like viral clearance claims
- Phase 1 pre-IND feedback for Pinnacle product:
  - “We note that many specifications have acceptance criteria of ‘Report Result’. We recommend that you leverage manufacturing data as well as product quality attribute data from the platform, engineering lots, and process development lots to set reasonable and quantitative acceptance criteria. Acceptance ranges should be progressively narrowed as product development continues, based on manufacturing experience.”
    - Specific feedback was also provided regarding viral protein purity and poloxamer content based on platform experience
  - “In your IND submission, please include any data supporting the viral clearance capability of the manufacturing process. This may include study reports for viral clearance studies conducted for similar AAV products using the same manufacturing process and/or clearance data obtained during development.”
- Take home message:
  - It’s difficult to justify using platform data for viral clearance but then not use it for specification acceptance criteria – Regulators prefer we use the platform data to set some sort of initial meaningful acceptance criteria even in early stages rather than “report results”

# Platform Control Strategies and Regulatory Feedback

Select Case Studies

# Evolution of Ultragenyx Gene Therapy Platform Control Strategies

| Attribute | Phase 1/2 Control Strategy | Phase 3/Intended Commercial Control Strategy |
|---|---|---|
| Identity | • Biological identity based on mRNA expression assay<br>• Genome identity based on transgene-specific ddPCR<br>• Capsid identity based on LC-MS | • For DP only: remove biological identity tests |
| Particle titer | • No acceptance criteria; "report results" | • Add acceptance criteria |
| Potency | • Expression assay (mRNA or protein expression)<br>• Infectious titer by $TCID_{50}$ | • Add functional potency assay<br>• Expression assay (mRNA or protein expression)<br>• Remove $TCID_{50}$ |
| Aggregation | • Test for DS and DP release and stability | • Remove test from DS stability |
| Empty, full, and partial capsids | • % empty acceptance criteria for release<br>• Collect data on all peaks (characterization only) | • % **full** acceptance criteria for release<br>• Continue to collect data on all peaks (characterization only through PPQs) |
| Extractable volume | • Phase agnostic: depending on manufacturing capabilities, rely on in-process weight checks only and do not test extractable volume on release | |
| Bioburden | • Phase agnostic: Test larger volume but only one media type (TAMC on TSA plates) | |
| CCIT | • Phase agnostic: platform decision regarding use of DP vials vs. buffer vials | |

# Platform Strategy Evolution: Removal of $TCID_{50}$ Testing for Late-stage Programs

| Attribute | Phase 1/2 Control Strategy | Phase 3/Intended Commercial Control Strategy |
|---|---|---|
| Potency | • Expression assay (mRNA or protein expression)<br>• Infectious titer by $TCID_{50}$ | • Add functional potency assay<br>• Expression assay (mRNA or protein expression)<br>• Remove $TCID_{50}$ |

- Acknowledgement that the method does have utility to support early phase programs especially where a relevant functional potency assay does not yet exist
- As programs advance and additional potency methods are implemented to assess potency downstream of infectivity (e.g., transgene expression, functional potency), the value of the $TCID_{50}$ method wanes
- Platform position and justification:
  - Replace method with more biologically-relevant functional potency method in Phase 3
    - Functional potency assays are more relevant for assessing product potency as they are the assays closest to ensuring efficacy in patients
  - Assay has higher variability; acceptance criteria span several logs and are often not well correlated with functional potency or expression assays (which are well correlated with each other)
    - For these reasons, the assay is not adequate for controlling product quality in late-stage development and for commercialization
  - The assay cannot be considered a sensitive stability-indicating method; on stressed and accelerated stability, expression and functional potency methods often exhibit a decline in potency at earlier time points compared to $TCID_{50}$
  - Maintain the method as an investigational tool to support potency investigations and comparability studies

# Regulatory Feedback: Removal of $TCID_{50}$ Testing for Late-stage Programs

- Feedback from 3 programs (note that one program only removed the testing at the DS stage thus far)
- FDA, PMDA, ANVISA: in agreement
- Some EU countries and EMA: not in agreement for removal from DP testing; feedback included the following points:
  - Infectious titer test required by Ph. Eur. 5.14 – specifically, infectious titer together with expression of genetic product and biological activity are all 3 required to be tested in the final lot
  - Consider assay necessary to calculate the P:I ratio (GC:IU), allowing assessment of functional particles
- Company position to satisfy global feedback (which was accepted by EU countries):
  - Keep test as a characterization test for release of all clinical batches and for annual stability timepoints – results will not go on CoA or be used for product disposition and stability data will not be used to support product expiry
  - Regarding the P:I ratio, justification was provided that the P:I ratio is no longer necessary and is not a reliable tool for monitoring functional particles
    - In some cases, a negative correlation can be observed between the P:I ratio and functional potency activity

# Platform Strategy Evolution: Bioburden Testing

| Bioburden | • Phase agnostic: Test larger volume but only one media type (TAMC on TSA plates) |
|---|---|

- Previous testing strategy: split smaller sample volumes between TAMC and TYMC due to batch volume constraints, but regulatory feedback required a shift in strategy
- Feedback from multiple EU countries across multiple programs:
  - Volume and specification for DS bulk harvest and DP pre-filtration step does not meet EU guidance (e.g., ≤1 CFU/10 mL)
- Company strategy shift:
  - Increase volume of testing but only test TAMC on TSA plates (single media type)
    - TSA plates provide a general growth medium that is non-specific which gives an indication of any contamination
    - Media will be incubated at median temperature of 20-25˚C for 3 days and then 30-35˚C for 2 days to ensure both bacteria and mold can be recovered
    - Incubation on one type of media ensures additional sample volume is minimized due to considerations around product yield
  - Small DS batch sizes justify smaller samples as justified in Ph. Eu. 2.6.12 which states that a minimum of 1% of the batch shall be tested if the batch is less than 1000 mL
- Feedback to date:
  - EU countries: in agreement
  - FDA: not in agreement yet until data are provided demonstrating that one type of media is sufficient

# Platform Strategy Evolution: Empty, Full, and Partial Capsids

| Attribute | Phase 1/2 Control Strategy | Phase 3/Intended Commercial Control Strategy |
|---|---|---|
| Empty, full, and partial capsids | • % empty acceptance criteria for release<br>• Collect data on all peaks (characterization only) | • % **full** acceptance criteria for release<br>• Continue to collect data on all peaks (characterization only through PPQs) |

- Previous testing strategy: control % empty capsids only as it is a more accurate measure of impurities
  - Justification:
    - Not all capsid characterization methods can separate or quantify the intermediate and full species, while the empty capsids are more readily separated from the DNA-containing species
    - Reporting % empty capsids in release testing enables more flexibility in method lifecycle management
    - % of all capsid species (empty, intermediate, and full) are still captured as part of product characterization
- Feedback from FDA for two Phase 3 programs:
  - Need to control % full and % intermediate capsids and not just % empty capsids
  - Determine how much material in full capsids constitutes the vector genome relative to other DNA contaminants
    - Will characterize capsid content and revise acceptance criteria ahead of BLA
- Feedback from EMA: request for additional Scientific Advice is warranted and expressed concerns over % empty capsid acceptance criteria
- Company strategy shift (submissions pending):
  - Set acceptance criteria for % full capsids for release instead of % empty capsids
  - Continue to collect data on all capsid species (empty, intermediate, and full) as part of product characterization
  - Characterize capsid content prior to BLA

# Conclusions and Recommendations

- Pinnacle platform and initial regulatory feedback allowed us to start thinking more broadly in terms of the advantages of platform approaches
  - This has evolved with increasing experience, knowledge, and regulatory feedback on a variety of topics
  - We can ensure new programs are ready for late-phase expectations even before Phase 1 – setting meaningful critical parameters and controls early on even with limited specific product batch data
- Evolution of platform control strategies naturally occurs with increasing knowledge, data, and external influences
  - Learn from successes and failures and apply that knowledge to the next program and don't be afraid to constantly refine your strategic platforms – they are expected to grow and evolve with new data and information
  - Regulatory feedback plays a role too; however, conflicting feedback across regions presents issues
    - Harmonization across regulators is key to applying platform approaches globally
    - Mutual recognition is also key to encouraging the use of platform approaches – the requirement to repeat testing in multiple countries/regions presents challenges in the ability to realize the full advantages of platform strategies

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