Roundtable Session 2 – Table 8 – How Are We Maximizing the Leveraging of Prior Knowledge and Platform Processes?

Facilitator: Aaron Beach, *Eli Lilly and Company*

Scribe: John Tukianen, *Intellia Therapeutics*

Abstract:

As CGT modalities mature and new approaches enter the clinic, platform knowledge represents an immense opportunity for sponsors to streamline regulatory filings and studies that would support accelerated development timelines, reduced redundant testing, and more efficient clinical entry for next-generation programs. FDA's 2024 Platform Technology Designation and recent Plausible Mechanism pathway have created formal mechanisms for leveraging prior knowledge across programs in the CGT space, but practical application of these frameworks is still in infancy. For modalities such as in vivo gene editing, AAV gene therapy, and ex vivo cell therapy, sponsors must balance the platforming of analytical methods, manufacturing processes, and stability claims against the reality that each new payload, target, or indication introduces program-specific risks that may still require de novo characterization.

This roundtable will discuss the industry perspectives on how organizations are operationalizing platform strategies in CMC filings. Participants are encouraged to share lessons learned from IND, BLA, and post-approval submissions. The goal is to takeaway best practices, common failure modes, and identify gaps in how the CGT industry leverages platform and prior knowledge to accelerate development of new gene therapies while still meeting health authority expectations.

Discussion Questions:

1. What scope of platform claims have you successfully made in IND or BLA filings, and where have they been pushed back on? Are there specific CQAs where platform data is reliably accepted, versus areas where program-specific characterization is consistently required? For those who haven't yet formally aligned on platform with regulatory agencies but are considering it in the future, are you still leveraging platform data informally in submissions, and what has been the successes/challenges?

2. When applying a platform analytical method to a new program, what is your minimum bridging package versus full validation? How do you navigate method transfer across test labs while preserving the platform claim?

3. When a platform process change is made (e.g. new raw material vendor, scale change, site transfer), how do you propagate comparability conclusions across multiple programs that share the platform?

4. How do EMA, PMDA, Health Canada, MHRA, and others view platform claims relative to FDA?

Notes:

Question	Discussion

1. What scope of platform claims have you successfully made in IND or BLA filings, and where have they been pushed back on? Are there specific CQAs where platform data is reliably accepted, versus areas where program-specific characterization is consistently required? For those who haven't yet formally aligned on platform with regulatory agencies but are considering it in the future, are you still leveraging platform data informally in submissions, and what has been the successes/challenges?	• Early distinction between prior knowledge and platform knowledge
	• With early phase programs, or entirely new modalities, what's worked? What have you been able to leverage across program?
	  ○ Agreement that platform approaches to method development has received little to no pushback when leveraging prior knowledge from similar products/modalities – as long as it is appropriately referenced and documented
	  ○ However, as soon as you start to sway from your platform approach and/or make changes to the method, it becomes increasingly difficult to reference prior knowledge
	  ○ General acknowledgement that residuals have seen consistent pressure testing by several agencies, when referring to prior knowledge or platform justification
	  ▪ Expectation that residual testing may need to be demonstrated on product level, regardless of available prior knowledge
	• Distinction between process related vs product related impurities and justifications for leveraging prior knowledge
	  ○ Example shared where process optimizations were made, and chemical additives should have been cleared based on prior knowledge, therefore prior knowledge supported no testing upon release
	  ○ Product related impurities can support use of prior knowledge as long as there is strong scientific justification
	  ○ Team agreed that the sooner you are able to identify where you may be able to leverage prior knowledge the better
	• Comment made about taking step back to level set on what is needed from prior knowledge and when/where it can be applied
	  ○ Is there a higher prevalence in earlier phases of development?
	  ▪ Yes, common in Phase 1/2 when knowledge about your process, methods, and product may be limited
	  ○ Example shared – allogenic program, same process, reagents, etc, but lenti was different
	  ▪ CMC information was leveraged from prior filing to reduce the content generation requirements for new filing

Question	Discussion
	▪ General characterization from that product was also leveraged ▪ Comment – that this can be applied across, but really depends on your product portfolio ○ Team agreed that if identical components used across program, should evaluate and be able to leverage prior knowledge • CDMO examples shared ○ CDMOs often have business platform applied across multiple programs regardless, and data is based on site history/successes across multiple programs and in most cases can be leveraged right from the very beginning ○ However, this is challenging for sponsors to be able to access this information as it is not owned by the sponsor ○ The question then becomes – how much data is available to the sponsor to make a convincing argument that your platform is supported based on CDMOs manufacturing platforms, or is it too unique to leverage their prior knowledge ○ Question from the table – as a CDMO, how much of this information can you provide to the client for platform technology? ▪ Clarification – if it's the client's data or CDMO – if it is CDMO generated, should be able to share, if it is specific to a client, no ▪ If the client wants to look at overall platform datasets, it is possible for CDMOs to redact information and share with clients • Report authoring ○ Plan to set up end game from the get-go ○ Don't want to jeopardize another program by tying one program to another, unless you want to lifecycle manage both programs in perpetuity ○ To do so, ideally want to be able to plan for this all at the beginning of program setup ○ May have to consider reauthoring reports/filings etc. to make them product specific to get around this, or in some instances generate product specific data • Moving platform processes/methods between sites/CDMOs/etc. ○ CDMO tech transfer ▪ If you own the data, you can transfer ▪ May need an agreement to license information you don't own ○ Sample handling prior knowledge can be lost

Question	Discussion
	○ Public knowledge for specifications ▪ Successfully leaned in industry does for certain attributes ○ General leveraging of public information is good, as long as you can make the argument for relevance
2. When applying a platform analytical method to a new program, what is your minimum bridging package versus full validation? How do you navigate method transfer across test labs while preserving the platform claim?	• Platform CEF methods ○ Successfully leveraged previous development for the new program ○ However, was shared that still wanted to see the impact to the new program • Cell line changes and comparability data package requirements ○ Based on prior knowledge of cell line, was able to limit testing requirements to deem comparable ○ Specific for product related impurities, had enough prior knowledge to mitigate in data package • Question on CDMO approach to platform analytical methods – how to approach when CDMO wants to use platform analytical method, but is unable to share data associated with the platform? ○ Supporting validation may be lean on data package – handled previously with agency communications directly between the CDMO and the agency, instead of providing the sponsor additional information ○ Challenge – when the supporting information is owned by the CDMO, it is difficult for the sponsor to "learn" anything about the method platform ▪ In some instances, paying for redacted information from the CDMO may be valuable here ○ Agreement that all of this needs to be well defined in quality agreements/CDAs between CDMO and sponsor • Example shared with partner projects/M&A ○ Due diligence needed by sponsor on what is provided when partners wholly take over program and/or program is purchased ○ A lot of internal prior knowledge may be lost • Leveraging stability data from one program to another ○ For certain process parameters, if successfully demonstrated may be possible to justify not reperforming stability if scientific rationale is sufficient and know that the CQA is not stability indicating ○ Can also be done based on risk assessment/paper exercise ○ Valuable for rare/ultra rare space when stability data poolability within one program may not be possible

Question	Discussion

3. When a platform process change is made (e.g. new raw material vendor, scale change, site transfer), how do you propagate comparability conclusions across multiple programs that share the platform?	• New raw material vendors
	  ○ Risk assessments may be performed and limited use testing
	• Raw material changes/vendor notifications
	  ○ How successful are companies negotiating back to vendor?
	  ▪ Example shared that it is possible to convince raw material vendor to make legacy product to prevent having to make changes for legacy program, comparability performed on newer programs
	• Lipid supplier changes
	  ○ Example shared that with lipid manufacturing process change, needed to implement analytical method changes/improvements
	  ○ However, with analytical method improvements, impurities became more resolved and appeared that impurities were growing with the “new” lipids
	  ▪ Needed to assess impact and then determine impact for other programs where this material was shared, as platform information leveraged
	• Questions specific to new draft FDA guidance on prior knowledge
	  ○ What level of prior knowledge can be implemented across program with starting material changes?
	  ▪ E.g. new amidite supplier, can use test for one program be applied across several depending on “like for like” – team agreed should be possible

4. How do EMA, PMDA, Health Canada, MHRA, and others view platform claims relative to FDA?	• General discussion on processes with very low yield
	  ○ If there is not enough material to put all batches on stability, how do agencies perceive this?
	  ○ One example shared that a program barely had enough material for characterization, stability, and the supporting clinical trial
	  ▪ Arguments should be made to leverage prior knowledge/platform knowledge in these instances to prevent duplicative stability studies – similar argument will probably have to be clarified in the future with increase prevalence of individualized therapies
	• For rare and ultra rare
	  ○ US seems to be the most flexible on the use of prior knowledge and platform claims
	  ○ UK and PMDA also seems to be up there in terms of flexibility, as long as there is sound scientific rationale

Question	Discussion

	• Based on discussions from previous conference days, it seems the agencies do already utilized prior knowledge/platform knowledge for vaccine strain updates
	• Experience with Health Canada:
	  ○ They typically agree with the application of prior knowledge/platform claims, but will want to see the supporting data for everything to make compete assessment
	  ○ Successful leveraging data across guide sequences
	  ○ One example shared – 3 programs that had 3 identical processes, data was shared for all 3 programs to support lesser number of PPQ batches, but they still pushed for 3 PPQ batches
	• Experience with PMDA
	  ○ More lenient when product is manufactured in Japan, but sponsors need to perform due diligence on what regions want to get into to mitigate this risk
	• General discussion on how this can all be subjective based on:
	  ○ Inter and intra departmental opinions within the same agency
	  ○ Differences between your regulator and background
	  ○ Regulatory capability
	  ○ Familiarity with cutting edge technology