Assays from Discovery to Deployment: Aligning Speed and Science with Regulatory Standards

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Panel

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Executive Summary

For teams advancing therapeutics from IND through late-stage trials, assay strategy should be treated as a development-critical decision, not a downstream validation exercise. This panel emphasized that assays must be intentionally designed to support specific decisions at each development phase. Misalignment between assay purpose and clinical or regulatory intent is a common source of late-stage risk. Both discussion participants and panelists emphasized that early and structured engagement with the FDA is one of the most effective tools for de-risking assay strategy before pivotal studies. Mechanisms such as Pre-IND, INTERACT, and Type C meetings allow teams to align assay selection, validation expectations, and data package needs well before Phase 2 or 3, when changes become costly or unrealistic.

For novel pathogens or programs without established correlates of protection or animal models, developers should plan for integrated in vitro packages that combine neutralization, functional, and, where appropriate, multiplexed approaches to support serological endpoints and/or manufacturing control. Importantly, when assay data and clinical outcomes diverge, the first step should be to reassess the assay itself rather than immediately modifying the product.

Topic 1: Polyclonal vs. Monoclonal Assay Development

The panel opened by examining how assay strategies differ between polyclonal and monoclonal therapeutics, using GigaGen's COVID-19 polyclonal antibody program as a case study.

Key Points

- Monoclonal antibodies require highly tuned assays that track specific circulating viral variants. Missing a variant can mean missing neutralization entirely.
- GigaGen's polyclonal product follows a regulatory pathway that is similar to a plasma-derived product, introducing unique regulatory considerations when compared to monoclonal pathways. The use of Integral Molecular's Reporter Virus Particles enable effective potency lot release assays to advance cGMP activities.

Consistency & Lot-to-Lot Comparability

- Consistency is assessed at the molecular level (antibody sequence diversity/repertoire analysis) and at the physicochemical level (cation exchange chromatography, charge, glycosylation).
- A tightly controlled manufacturing process is essential to achieving lot-to-lot reproducibility for a complex, diverse product. Use of a functional readout is critical to capture potency for polyclonal therapeutics.

Topic 2: Early FDA Engagement

A consistent theme throughout the session was the widespread hesitation among developers to engage with the FDA early in the development process. Both the panel and working group participants discussed the high perceived risk to early FDA engagement for smaller biotechnology firms, especially those attempting to de-risk therapeutics prior to licensing or acquisition.

Perceived Barriers to Early Engagement with the FDA

- Time and effort required to prepare a briefing package (even when internal data already exists).
- Fear that the FDA will say 'no' and require redoing work from scratch.
- General perception that agency interactions are slow and burdensome and could derail progress for companies moving toward exit (licensing product to a larger company or acquisition).
- Organizations are too busy and early engagement is deprioritized.

Arguments for Early FDA Engagement

- Several working group participants, including those who have worked in regulatory groups, discussed the culture of fear around FDA engagement and noted multiple low-barrier interaction mechanisms that are underutilized, including:
    - INTERACT meetings
    - Pre-IND consultation program
    - Meetings for IND amendments
- One participant from a regulatory group at a pharmaceutical company observed that developers who avoid early engagement often arrive in Phase 3 with a new, unvalidated assay and face rejection. Proactive early engagement reduces the risk and impact of late-stage issues.

Practical Observations

- A participant noted a case where a client at University of Rochester engaged the New York State Department of Health (rather than FDA) and received approval within months, using thousands of samples for robust validation. A parallel FDA submission by another company took nearly a year.
- Along with sample volume, sample diversity was identified as a critical factor in FDA approval timelines for serological assays.
- Sheila noted that AI tools may eventually reduce the effort required to compile briefing packages.

Topic 3: Assay Strategy with Novel Pathogens / No Correlate of Protection

The panel explored a scenario involving a novel pathogen where animal models do not reliably predict human outcomes, and where access to these models may be limited due to an influx of research interest.

COVID-19 as a Model Case

- Access to hamster in vivo models was highly sought out but practically inaccessible for many labs during early COVID development.
- The FDA ultimately did not require an in vivo protection model; neutralization assays were accepted as the primary surrogate and provided comprehensive data on product consistency and activity. GigaGen, alongside many others used Integral Molecular's Reporter Virus Particles to efficiently generate neutralization data.

Broader Challenges — Difficult Pathogens

- Many pathogens lack any practical in vivo model accessible outside of heavily funded or specialized BSL-4 settings.
- Sheila proposed a multi-pronged in vitro approach for such pathogens, incorporating neutralization assays and cell-mediated assays for a more comprehensive functional picture.

New Assays

- Multiplex platforms can be configured on a faster timeline to assess neutralization against multiple COVID variants simultaneously and offer significant flexibility for rapidly evolving pathogens.
- Broader FDA acceptance of multiplex platforms, particularly for generating functional data, remains an ongoing challenge compared to standard single plex binding assays such as ELISAs.

Topic 4: Non-Animal Models & New Approach Methodologies

The panel discussed the potential and limitations of organoids and other non-animal methods as regulatory tools.

Cautious Optimism for Organoid Approaches

- A participant acknowledged concern about what is lost when reducing complex immune responses to organoid systems, but noted that with clearly defined questions, organoids could yield actionable answers.

Current Regulatory Constraints

- Sheila highlighted an ongoing challenge: the FDA currently requires mouse neutralization assays, PK studies, and other applications that require the use of animals.
- Alternative PK/tox approaches are not accepted because they may not capture complex mechanisms of action involving interactions across multiple physiological systems or immune components.
- Organoids could theoretically replace or supplement traditional mouse assays, but concerns about relevance, reproducibility and normalization remain.

Topic 5: Marginal Phase 2 Efficacy & Strain Mismatch Scenario

The panel presented a scenario in which clinical efficacy of a vaccine in Phase 2 was 70%, with no established correlate of protection for the pathogen, and infections driven by newer circulating strains associated with lower serum titers in vaccinees.

Assay vs. Antigen

- Sheila leaned toward re-examining the assay rather than immediately assessing the antigen/epitope.
- A participant from AstraZeneca recommended first verifying that the trial population was representative of the broader population since localized demographic or unusual strain distribution might explain the discordance without requiring product changes.
- Incorporating local epidemiological strain data into a more comprehensive assay was seen as a logical next step.

Strategic Considerations

- 70% clinical efficacy is substantial, and doesn't necessarily warrant a new correlate. Rather, the assay's purpose should be reassessed to determine if it is meant to serve as a marker of efficacy or as a manufacturing control.
- For rapidly evolving pathogens, consider whether the product demonstrates consistent efficacy across seasons (analogous to flu vaccine trials) rather than optimizing against a single strain.
- Retained samples from Phase 2 could be used to explore alternative immune response metrics before committing to a Phase 3 strategy.

Topic 6: What Does It Take to Go First?

The session closed with a discussion on the incentives and barriers to being the first group to try a new assay approach, in generating data for regulatory processes.

Key Perspectives

- Participant from AstraZeneca: Capital is the primary de-risking tool. The ability to absorb failure makes risk-taking possible. Innovation is most accessible to well-funded organizations, or startups with high risk tolerance.
- Participant from Merck: Money alone is insufficient and scientific conviction is equally essential. Deep understanding of why a new approach is better must precede investment. Large companies with long-term product commitments are inherently more willing to invest early while smaller companies targeting acquisition are less likely to do so

- Sheila: Regulatory clarity from the FDA would help, as would an urgent threat (novel pathogen) as an external forcing function.

Key Takeaways

- Engage the FDA early because the fear is disproportionate to the actual risk. Pre-IND and Type C meetings are underused tools.
- Assay strategy must be matched to the product modality (polyclonal vs. monoclonal) and the regulatory pathway.
- For novel pathogens without animal models, a combination of neutralization and functional in vitro assays can build a credible regulatory package.
- Multiplex platforms offer greater flexibility but face a barrier of more complex controls and adoption challenges at the FDA compared to simpler single-plex approaches.
- Clinical efficacy data always takes precedence. When assay results conflict with clinical outcomes, revisit the purpose of the assay before considering product redesign.
- NAMs and organoids hold promise but require improved reproducibility and normalization before broad regulatory acceptance.
- Moving forward with novel technologies requires capital, conviction, and a clear public health imperative.

About Virology at Integral Molecular

Virology at Integral Molecular is a business unit of Integral Molecular, a company founded by virologists in 2001. Our mission is to develop and apply innovative technologies that advance therapeutic discovery against difficult protein targets, including viral proteins. From basic research to vaccine clinical trials, our virology products support work across a diverse range pathogens, including influenza, SARS-CoV-2, dengue, and more. We support leaders in virology from initial project concept to reagent and assay design, to expert interpretation of results. Deep expertise in virology remains at our core. We've developed technologies that have enabled hundreds of companies worldwide working in vaccine research and drug discovery. Our technologies have been published in over 500 papers and patents, including articles in Cell, Science, and Nature. Learn more about Integral Molecular and our Leadership team.