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Integrated Biologics

Article

Why early immunogenicity assessment is critical to biologic development

An article from **Early Development Services**,
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In biologics development, a molecule can look highly promising on paper and still fail because the immune system does not tolerate it in the way the program anticipated. A strong mechanism of action, good target engagement, and encouraging early potency data do not remove the need to evaluate immunogenicity rigorously. In fact, as biologics become more complex and molecular formats continue to diversify, early immunogenicity assessment becomes even more important because safety-related liabilities may be embedded in the molecule itself, in its sequence-derived features, or in product-related attributes that only become visible when development work begins in earnest. Safety and immunogenicity issues contribute to a substantial proportion of failures, while early-stage programs also operate under tight funding and high CMC expectations.

Immunogenicity is not just a downstream regulatory consideration. It is a technical development issue that can influence candidate selection, molecular engineering strategy, assay strategy, IND readiness, and ultimately the probability of clinical success.

Immunogenicity sits within a broader early development framework focused on understanding and mitigating potential risks associated with a molecule. Within this framework, immunogenicity testing helps identify and characterize immune-related risks, alongside other assessments that collectively contribute to the molecule's overall risk profile.

At Lonza, we position immunogenicity risk assessment within our immunosafety offering, alongside immunotoxicity evaluation, because understanding immune-related risks is complex and typically requires a multiple complementary assessments.



What immunogenicity means in technical terms

Immunogenicity is the ability of a product to trigger an immune response. In the clinical setting, this is typically assessed by measuring anti-drug antibodies (ADAs) in patient serum, often using ELISA-based assays. These ADAs may be either binding or neutralizing, and the distinction matters. Binding ADAs can sometimes be clinically manageable, whereas neutralizing ADAs may directly impact pharmacokinetics, alter exposure, or compromise safety and efficacy.

In early development, immunogenicity risk should not be viewed only through the lens of a future clinical assay. It must be understood mechanistically. Lonza's immunosafety services can be used to assess the risk of immunotoxicity, innate and adaptive immune response, with assays designed to assess immediate responses linked to product mode of action, short-term responses caused by product- or process-related impurities, and longer-term responses associated with naïve CD4+ T cell activation and ADA generation. This layered view is scientifically important because immunogenicity is rarely driven by a single factor. It can arise from the protein sequence and structure, product and process-related impurities, the mode of action, or even unintended off-target interactions with the immune system.

Why early immunogenicity assessment needs both prediction and experimental validation

Immunogenicity assessment should begin early and combine predictive and experimental methods. Lonza's *in silico* approach uses the Epibase® platform to identify potential T cell epitopes and rank molecules by factors such as epitope content, human leukocyte antigen (HLA) binding affinity, HLA binding promiscuity and HLA allele frequency. These rankings can then be benchmarked against marketed molecules, helping teams compare candidates and select the lowest risk lead to take forward.

This type of sequence-based evaluation is technically valuable because it allows developers to rank candidates before locking into one sequence or molecular format. If a candidate carries a high burden of potential T cell epitopes, or if liabilities cluster in a functionally important region, teams can consider engineering options earlier, including humanization, deimmunization, or broader reformatting. Lonza's protein engineering workflow supports this process through framework selection, grafting of regions of interest, manufacturability assessment, Epibase® guided deimmunization, and experimental validation of the redesigned molecule.

However, sequence-based prediction alone is not enough. Lonza's immunosafety platform complements *in silico* analysis with a broad set of *in vitro* human immune cell assays, allowing risk to be tested from multiple biological angles rather than inferred from sequence alone. Typical assay formats include:

- Peripheral blood mononuclear cell (PBMC) activation and proliferation assays
- Dendritic cell (DC):CD4 proliferation and re-stimulation assays
- DC uptake, DC activation and MHC-associated peptide proteomics (MAPPs) assays
- Whole blood and PBMC co-culture immunotoxicity assays

Why human-relevant assays matter

Preclinical immunogenicity assessment has historically relied on animal models, but these models are often poor predictors of the human immune response. As a result, the field has shifted toward fully human *in vitro* systems, supported by growing regulatory interest in new approach methodologies (NAMs).

This shift is more than a policy trend; it has direct implications for data quality and decision-making. Lonza supports

human-relevant assessment with highly diverse PBMC banks containing several hundred healthy donors at any given time. All donor PBMC are HLA typed at HLA Class I & II alleles to at least 4-digit (high resolution) with matched serum samples and a stringent quality control which includes post-thaw viability, cell population analysis and an assessment of T cell functionality. This infrastructure is what separates a superficial assessment from one that is genuinely informative and representative of the target population. Meaningful evaluation of human immune response requires not only the right assay format, but also high quality, well-characterized human samples and the expertise to interpret donor variability and assay outputs appropriately.

Expertise is therefore a decisive factor. Lonza has experience across a wide range of molecular classes, including monoclonal antibodies, antibody-drug conjugates (ADCs), antibody fragments, multispecifics, recombinant proteins, vaccines, immunotherapies, and cell and gene therapy products. Its work also spans applications such as lead selection, risk assessment, impurity studies, post-translational modification analysis, protein engineering, humanization, deimmunization, and immunotoxicity evaluation. That breadth matters because immunogenicity risk is highly context-dependent. The right assay strategy for a monoclonal antibody is not necessarily the right strategy for a T cell engager, an ADC, or a recombinant protein.

How early immunogenicity assessment improves outcomes

The value of early immunogenicity assessment is not that it assigns a simple risk label, but that it creates opportunities for intervention while change is still practical. Lonza's early drug development decision-making framework (Figure 1) links *in silico* sequence analysis to liabilities such as PTMs, aggregation, and immunogenicity, then maps possible responses including re-engineering, further testing, additional monitoring, or progression to a backup candidate. The intended outcome is especially important: a biologically active, developable molecule. This is the practical advantage of doing the work early.

When risk is identified while a molecule is still in a flexible phase of development, teams can adjust sequence design, candidate selection, or supporting evidence before later stages lock in complexity and cost. Lonza's EDS workflow shows how immunogenicity assessment can be integrated with developability and manufacturability assessment, protein expression, and other early de-risking activities. This enables risks to be evaluated iteratively as molecules progress, rather than addressed through isolated, late-stage assessments.

Early development work also supports more realistic estimates of timeline and cost, strengthens the case for program funding, and helps smooth progression into IND-enabling studies. These benefits apply directly to immunogenicity assessment because unresolved safety liabilities are precisely the kind of uncertainty that can weaken a program both technically and strategically.

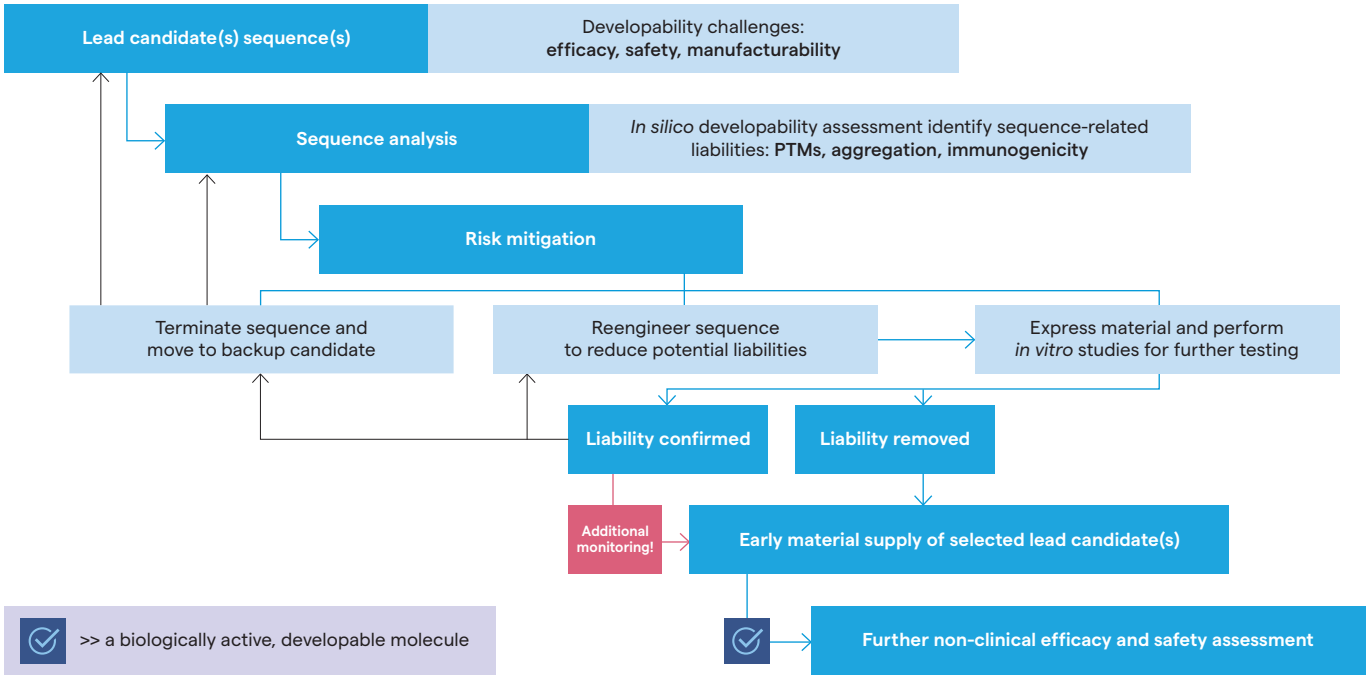


Figure 1
De-risking of early drug development; decision making tree for biotherapeutic candidates.

Early immunogenicity assessment is a core discipline in building safer, more developable biologics

Early immunogenicity assessment is critical because immune risk is one of the most technically complex and clinically consequential challenges in biologics development. It sits at the intersection of sequence design, product quality, assay science, immunology, and regulatory filing. Lonza's Early Development Services address this challenge through an integrated strategy that combines *in silico* prediction, human-relevant *in vitro* testing, immunotoxicity evaluation, and the expertise required to interpret results in the context of the specific molecule under development.

For biologic drug developers, the technical outcome is clear: early immunogenicity assessment improves candidate selection, supports rational engineering and de-risking, strengthens the evidence base for later development decisions, and reduces the chance that avoidable immune-related liabilities will emerge only after substantial time and capital have already been committed. In that sense, early immunogenicity assessment is not simply an additional study, it is a core technical discipline in helping to build a safer, more developable biologic.

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