International Alliance for Biological Standardization

10th Annual Statistics Workshop: Science & Statistics – Elevating CMC through Partnership

November 12-14, 2024
IBBR, Rockville, USA

A patient-centric approach to cell therapy manufacturing: Linking CAR-T product attributes and CQAs to clinical outcomes

CAR-T cell therapy has demonstrated a high rate of durable responses and a manageable safety profile in patients with adult relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL), follicular lymphoma and pediatric acute lymphoblastic leukemia (r/r pALL).

In cell therapy, each batch represents a unique patient which translates to a very high batch to batch variability. Thus, cell therapy needs to manufacture a consistent final product that reliably meets release specifications from a very heterogeneous incoming patient material (apheresis). Given that the cell therapy product is basically the patient's own cells, the link between product attributes and clinical outcomes becomes essential. Relating the apheresis and final product characteristics to manufacturability, clinical efficacy and safety is key to refining our understanding of critical quality attributes (CQAs), specifications and any potential improvements to this breakthrough therapy.

During Novartis' ELIANA (r/r pALL) and JULIET (r/r DLBCL) clinical trials, each batch was extensively characterized for cell composition (immunophenotypes) and final release criteria. This produced a high dimensional dataset where the number of variables exceeds the number of observations. Statistical and machine learning methods (e.g. LASSO/elastic net, random forest, decision trees, logistic and COX regressions) were applied to elucidate which immunophenotypes and CQAs for the CAR-T products may be of significance.

Results from these multivariable analyses revealed subsets of parameters associated with the response. Different sets of variables were identified for the pediatric and adult indications. The immunophenotypes and CQAs that were teased out help inform future development and provide insights into the manufacturing and control strategy. Importantly, the analyses also confirmed that the manufacturing process can handle the highly varied starting material and consistently deliver quality final product to the patients.

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Statistical assessment for analytical comparability between pre-change and post-change processes.

On behalf of Aili Cheng and the NCB comparability workstream:

The FDA draft guidance on "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products" (2023) recommends statistical approaches such as quality ranges and equivalence tests to assess manufacturing analytical comparability between pre-change and post-change processes. The Critical Quality Attribute (CQA) data underlying such analyses in the fields of cell and gene therapies are highly variable and usually have a limited number of batches. Thus, it is a challenge to demonstrate comparability with enough statistical power. Furthermore, the CQAs may not always follow a normal distribution and the standard approaches which assume normality may not be optimal for these data. Naively applying quality ranges and equivalence acceptance criteria (EAC) solely based on some multiplier of standard deviation (SD) could lead to misleading results, with safe and effective products being discarded. This presentation will focus on key topics relating to comparability in cell and gene therapy, such as study design, acceptance criteria, sample size and important assumptions about the distributions of the data. Additionally, insights from correlational analyses between CQAs and clinical outcomes can be leveraged to assess whether or not the observed ranges and/or results of comparability studies may be meaningful from a practical, scientific and clinical perspective.