Roundtable Session 1 – Table 6 – Setting Specifications for Autologous CAR-T Cell Products Given the Inherent Patient to Patient Variability of the Apheresis Starting Material

Facilitator: Jessica Eisenstatt, *AstraZeneca*

Scribe: Kerin Ablashi, *Biologics Consulting*

Abstract:

Autologous Chimeric Antigen Receptor (CAR)-T cell products are growing in use for immunotherapy and cancer treatments. In autologous CAR-T cell products, patient-derived T-cells from apheresis material are isolated and genetically modified to express a target antigen. The drug product is then administered back to the patient after release testing. Unlike allogeneic products in which a healthy donor provides starting material for multiple patients, the donor material for autologous products will be from patients and differ for each manufacturing batch. From establishing release specifications for first time in human studies to commercial products, Sponsors need to consider the inherent patient-to-patient variability of starting material and its effect on the final drug product. Prior to starting a clinical trial, pre-clinical studies are performed with healthy donor starting material. When setting specifications from this material, the potential for differences in test results from patient starting material for assays such as viability, identity, and potency needs to be considered. As clinical trials proceed through later phases, Sponsors may adjust specifications based on patient batch data, and manufacturing history which may be complicated by the patient-to-patient variability. We will discuss considerations taken when setting specifications for autologous CAR-T cell products, how analyzing patient starting material can aid in establishing specifications, and how we see autologous CAR-T cell product development in the future.

Discussion Questions:

1. What considerations do Sponsors need to take when establishing specifications based on healthy donor material, as a surrogate to patient starting material, in pre-clinical studies for CAR-T cell products when planning a first time in human study?

2. Specifications such as cell viability, potency, identity can vary based on donor material. Throughout development, how can Sponsors and health authorities work together to ensure product safety and efficacy for patients?

3. How are health authorities outside of the US FDA addressing the use of healthy donor starting material as surrogate starting material and the patient-to-patient variability when setting release specifications?

Notes:

- Genome integrity testing is required by Ph. Eur.

- Even if sponsors plan to start with a US-centric submission, recommend considering global requirements early to make things easier later in development.
- For autologous products, is the panel of tests needed for donor screening less because the material will be going back into the same patient?
- Are there different expectations for different types of cell therapies?
- Challenges
    - Setting specifications is difficult – it is difficult to apply specs for material from healthy donors to materials from patients, so specs have to be based on prior knowledge and early research results. Also consider method ranges and method capabilities.
    - What range is is too wide for specs?
    - If you set a specification then find that it needs to be lowered or widened, will the Agency be flexible and allow the change? Supporting data are needed to justify the change.
    - Using 2 sided vs. 1 sided potency specs? The spec helps predict clinical efficacy.
    - Unlike with monoclonal antibodies, CAR-T products (e.g.) can't compare their materials to a reference standard.