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Bioanalysis of Biotherapeutics

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Obtaining relevant and accurate information on pharmacokinetics (PK) and exposure for biotherapeutics is one of the key fundamental elements in research and development (R&D) process. Typical R&D process if often described in several steps starting with discovery phase continuing through several development phases. In the early discovery phase, multiple candidates or even various modalities of the drug in development are evaluated, including comparison of the PK properties. As an example, half-life for a monoclonal antibody (mAb) or a Fc-fusion compound may be compared to a typical mAb based drug or the impact of a specific mutation designed to improve compound PK properties are assessed. Appropriate description of the PK properties for a biotherapeutic requires access to solidly developed bioanalytical methods with high specificity, selectivity and sensitivity allowing for evaluation of drug concentrations. Any protein based biotherapeutics is expected to carry various degree of immunogenicity risk therefore requiring an in study assessment of immunogenicity response. Well designed and high quality bioanalytical strategy therefore enables an effective understanding of the exposure-response relationship including assessment of toxicity and efficacy.

Current state of the biotherapeutic research presents a great diversity of biotherapeutic modalities that translates into a variety of bioanalytical challenges and multiplicity of analytical platforms. Bioanalysis of biological drugs has conventionally utilized Ligand Binding Assay (LBA) platforms. The typical enzyme linked immunosorbent assay (ELISA) method continues to remain the workhorse of a bioanalytical lab. Newer technologies have come forward, are maturing or starting to emerge, including label free Surface Plasmon Resonance applications, high throughput Gyros®, high sensitivity Erenna Immunoassay Technology® by Singulex, immunoPCR systems by Imperacer® or digital LBA SiMoA platform developed by Quanterix.

A number of alternative scaffold based biotherapeutics have been recently introduced. One of the ideas that have been proposed several decades ago has materialized with two antibody-drug conjugates (ADCs) compounds achieving regulatory approval status [1]. ADCs materialize a promising combination of large mAb based biotherapeutic with a low molecular weight drug toxin. The complexity of the ADC structure translates into the need for a multi-analyte approach to describe appropriate PK properties. As a result, various analytical platforms have been used, including LBA, LCMS/MS and combination of the two [2]. Importantly, bioanalytical questions raised during the ADC development process differ depending on the compound research phase. As an example, early discovery support may require a qualitative relative investigation of the drug to antibody ratio while later, during clinical development phase; a quantitative assessment of the conjugated drug concentration may be requested. Both may be done by utilizing LCMS technologies but will require different type of equipment and analytical skill set. In general, LCMS technology has emerged as a highly valuable platform with potential for characterization, qualitative and quantitative assessment of large molecule based compounds [3].

ADCs present an interesting instance of the differentiation between expectations and requirements placed in front of a bioanalytical scientist when supporting biotherapeutic at different phases of development. Recent ADC bioanalysis position paper [4] describes several applicable analytes and recommends seeking a correlative relationship between exposure and efficacy/safety signals. It also highlights that the collection of most appropriate analytes may be specific for a given ADC compound. Bioanalytical investigations conducted during early discovery phase therefore may define the need for greater investment in the measurement of specific analytes in later, development phases.

Central to the process of the bioanalytical strategy design is therefore the decision about the analyte to be detected in the PK assay. As an example, for mAb based compounds with a soluble or shed molecular target, it is important to determine whether the project requires detection of free (from the bound molecular target) vs. total drug [5]. As such information is generated early in the life cycle of the project, it will be carried on to the next discovery and development stages. It is important to consider that continuum of PK information will assist project progression and avoid conduct of unnecessary and redundant studies.

Industry White papers and regulatory guidance documents list a number of tests to be performed in order to demonstrate quality and appropriateness of a bioanalytical method [6,7]. These include evaluation of the assay precision and accuracy, specificity and selectivity, robustness and ruggedness, dilutional linearity and parallelism and reference material stabilities. These guidance defined criteria are applied for the development stage bioanalytical protocols, specifically used in support of regulated non-clinical and clinical studies. Is has been argued that at the discovery stage, PK assays face numerous limitations, including a lack of appropriate reagents as well as resources and time shortage [8]. Is it suggested that as the goals of discovery investigations differ from the goals set during development phases, the accepted analytical error applied [9] in the early stage of project development could also differ, i.e. a fit-for-purpose approach is encouraged. For example, when a discovery study is targeting to determine a large difference between PK properties for two drug candidates, a relatively broad acceptance criterion for bioanalytical methods may be accepted [8]. Regardless of the limitations, availability of high quality data is critical at all stages of development. Hence, it becomes the challenge of a bioanalytical scientist to determine appropriate scientific justification and data value-driven approach to the scope and the degree of discovery assay qualification. Often a flexible analysis of a mix of pre-study and in-study assay performance and reliability data can be applied [8]. It should be understood though that some tests, e.g. matrix stability of

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the reference material, assay selectivity and specificity [10] and other require deliberate evaluation and may not be easily inferred from in-study data directly. Bioanalytical scientists need to recognize the future use of the PK information developed during discovery stage and of the assay itself. Discovery assay capabilities and limitations need to be understood and communicated. As the project continues to progress through the stages of development, the rigor of assay qualification/validation and the requirements for the assay data quality will increase. To ensure reliable and consistent ability to compare data between discovery and later development stage studies, a continuum in the assay quality is highly desired.

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