Guidelines for Validation of Immunogenicity Analysis of Anti-drug Antibodies

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ABSTRACT

Abstract:
Almost all biopharmaceutical products can cause certain anti-drug antibody (ADA) reactions. Anti-drug antibody reactions may reduce drug efficacy or lead to serious adverse reactions. Anti-drug antibodies usually do not cause significant clinical reactions in humans. However, for some therapeutic proteins, the anti-drug antibody reaction can cause a variety of clinical adverse reactions, including mild events and serious adverse events. Pre-clinical studies have shown that anti-drug antibodies can affect drug exposure, toxicity, pharmacokinetics and pharmacodynamics. Therefore, the immunogenicity of therapeutic proteins has caught the attention of clinicians, pharmaceutical companies and regulatory agencies. In order to evaluate the immunogenicity of bio-drug molecules and link the experimental results with clinical events, it is necessary to develop reliable experimental methods to effectively evaluate the anti-drug antibody response in pre-clinical and clinical studies. Methodological validation is particularly important here, and methodological validation is essential for drug listing applications. Current regulatory documents have limited guidance on the validation of immunoassay methods, especially the lack of guidance on the validation of immunogenic assays. This paper provides scientific suggestions for the validation of immunoassay methods for anti-drug antibodies.

Introduction:
Biopharmaceutical products, including amino acid polymers, carbohydrates or nucleic acids, are generally expressed through human cell lines, mammalian cells or bacteria, which are larger than conventional small molecular drugs (generally larger than 1-3KD). Because of the above characteristics, biopharmaceutical products have greater potential to induce an immune response. Immunogenicity of biopharmaceuticals and intrinsic factors of products (species-specific epitopes, exogenous, glycosylation, degree of aggregation or denaturation, impurities and preparations), external factors (route of administration, chronic or acute administration, pharmacokinetics and endogenous equivalent), patient factors (autoimmune diseases, immunosuppression) It is related to alternative therapy.

Anti-drug antibody reactions may lead to severe clinical symptoms, including allergies, autoimmunity and different pharmacokinetic characteristics.

Drug-induced immune response is an important indicator of drug safety and efficacy, which is also a common concern of regulators, manufacturers, clinicians and patients. Therefore, the Food and Drug Administration of the United States and the regulatory bodies of the European Union, Japan, Canada, Australia and other countries require the evaluation of anti-drug antibodies by pharmacological or toxicological methods. The relationship between immunogenicity and clinical symptoms depends on the objective detection and characterization of anti-drug antibodies in preclinical and clinical studies. Therefore, the immunogenic biological analysis method should be properly developed and validated before it can be utilized to detect research samples. Existing publications provide guidance on strategies, methodological development and Optimization for the detection and characterization of anti-drug antibodies. Methodological validation is the evaluation of analytical methods. Specific laboratory methods show that the analytical methods used are suitable for the corresponding detection requirements. Specifically for the detection of anti-drug antibodies, verification means that the method can reliably detect low levels of drug-specific antibodies in complex biological matrices (serum or plasma), such as consistency and repeatability. Methodological validation should be carried out in two stages: the pre-research stage refers to the work before the analysis of samples, the research stage refers to the analysis of samples, and the pre-research stage and the research stage are equally important to show the validity and controllability of analytical methods.

Method

1. Anti-drug antibody detection_ Clinical and non-clinical studies usually evaluate the immunogenicity of drugs by detecting and characterizing the anti-drug antibody response induced by treatment. At present, many methods can be used to detect anti-drug antibodies, including enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), Radioimmunoprecipitation (RIPA), surface plasmon resonance (SPR), electrochemiluminescence (ECL). Each detection method has its advantages and limitations, which have been discussed in recent articles. No matter what method is adopted, formal methodological verification should be carried out after the development and optimization of the method to ensure that the method is suitable for the corresponding detection requirements. Therefore, it can be predicted that the validation recommendations of this guideline are applicable to most of the anti-drug antibody immunoassays. Researchers should determine appropriate methodological validation schemes based on the characteristics of the detection system.

Anti-drug antibody detection methods are usually non-quantitative (sometimes semi-quantitative) tests, because there is no standardized species-specific anti-drug antibody available as a calibration standard [15]. Positive controls are generally internally developed (e.g. monoclonal antibodies or high immune serum polyclonal antibodies), and it is impossible to use all the anti-drug antibodies detected by subjects as positive controls. If a quality unit is to be used to mark the level of the anti-drug antibody, the parallelism between the standard and the test sample should be proved to determine the accuracy of the concentration of the sample [8,10]. If the parallelism between the sample and the standard is not proved, the accuracy is doubtful. Titration is another method for evaluating antibody levels. It is easy to lack parallelism between dilutions of different samples. However, it is noteworthy that previous studies have shown that titration is suitable for the evaluation of antibody levels. For decades, this method has been used in clinical infections, diagnosis and treatment of autoimmune diseases, and vaccination. Comparison of Anti-drug Antibody Reactions by Titration, it is simpler and requires less verification because it does not need to describe and prove in detail the parallelism between the anti-drug antibodies of different products and the standard products.

2. Application of Statistics

Reducing the subjective role in the verification process is one of the key points of this paper. In order to ensure the objectivity of the experiment, we must rely on statistical means. Since most researchers are unable to obtain the services of statisticians, this paper provides a simple and sufficiently rigorous and effective statistical method. All the statistical calculations involved can be calculated by commercial statistical software, and no experienced statisticians are needed in the calculation process. However, if statisticians assist in the design of validation experiments and data processing, the application of statistics may be more rigorous and effective than that provided in this paper.

3. Pre research validation

Validation tests in clinical and non-clinical studies before sample bioanalysis are called pre-study validation, which mainly describe the performance characteristics of analytical methods in mathematical and quantitative aspects [8]. Prevalidation refers to the preparatory work before the start of the research work, which can not be confused. On the other hand, research validation refers to monitoring the performance characteristics of the whole process of using the method to ensure the validity of the method and the reliability of the data. After developing and optimizing the whole method, the analysis method should have the condition of verification. For example, optimizing the test data shows that the detection method has potential reliability and is suitable for the corresponding detection requirements. The reliability of the method depends on the normal operation of the analytical equipment and computer system and the proficiency of the experimenters.

In essence, analytical methods are a holistic system with multiple factors, not just reagents. The validation method should include system applicability, which belongs to the research validation category.

It is suggested that a validation experiment program or SOP should be established before preliminary research and validation. The validation experiment program should explain the expected purpose of the method, the detailed description of the analysis method, the performance characteristics to be validated and the expected acceptance criteria of precision, robustness, stability and durability. In addition, it is suggested that appropriate experimental details and data processing steps should be added to the validation scheme, so as to provide a clear guidance for validators to ensure better data processing.

The acceptance criteria should be established for the detection of anti-drug antibodies, which can help to ensure the validity of the test in the research stage. Therefore, the system applicability criteria (acceptable range) for quality control should be established after statistical evaluation of the data obtained in the verification process. In addition, there should be acceptance criteria for reference substances and samples in the intermediate precision test during the research and verification stage. When the analysis data in the research and verification stage does not meet the acceptance criteria, the data should be rejected. Acceptance criteria should not be established in the pre-research and verification stage, because it may exclude some validation data, resulting in inaccurate estimation of analysis errors. In addition to the clear reasons (such as technical errors) and intentional or unintentional deviations from the experimental scheme, all analytical data in the pre-research stage should be included. At present, the FDA, ICH and the guidance documents of the American Pharmacopoeia elaborate the general performance characteristics that should be studied in the analysis and validation of quantitative testing [23-25]. Because the immunoassay of anti-drug antibodies belongs to semi-quantitative detection, some requirements are not inapplicable. To verify the immunoassay method of anti-drug antibody, the following nine parameters should be determined: screening critical point, confirming critical point, sensitivity, acceptance standard for system applicability control (QCs), drug resistance, precision, robustness, stability and durability.

Related product:
anti-idiotypic antibody

EXTERNAL LINK

https://www.creativebiolabs.net/anti-idiotypic-antibody_71.htm

PROTOCOL STATUS

Working

We use this protocol in our group and it is working