Resolution of Drug Tolerance Issues Encountered with an Immunogenicity Assay

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Abstract

Human IgG4 therapeutics present a challenge to drug tolerance as they have a long half-life and high doses. Anti-drug antibodies can affect both safety and efficacy of the drug, and accordingly, assessment of their immunogenicity must be evaluated. Since most adverse responses are characterized by humoral immune responses, measurement of circulating ADA is a standard for assessment of immunogenicity. The FDA guidance recommends a minimum sensitivity of at least 100 ng/mL and a dynamic range of 70-3000 ng/mL. However, not all antibodies are coated directly to the plate for detection. Despite the additional sample handling steps, the assay yields a sensitivity of 25 ng/mL and increased drug tolerance to 200 µg/mL at the 100 ng/mL PC level. The PandA method yielded a sensitivity of 3 ng/mL and increased drug tolerance to 200 µg/mL at the 10 ng/mL PC level. The bead based method yielded a sensitivity of 0.48 µg/mL and increased drug tolerance to 60 µg/mL at the 100 ng/mL PC level, and <1 µg/mL at a 10 ng/mL PC level, which was not observed in the other methods. The bead based method was not inhibited by a 200 µg/mL concentration of protein A drug, whereas the other methods were inhibited. The PandA and Bead methods were not inhibited by a Co-administered Drug.

Methods

Bridging Assay

Adaptations of the ACE-Bridge assay were developed for a drug compound required improvement in drug tolerance due to high levels of the drug in clinical trial subjects. The results from those efforts are presented and discussed.

Results

An immunogenicity assay developed for a drug compound required improvement in drug tolerance due to high levels of the drug in clinical trial subjects. The results from those efforts are presented and discussed.

Conclusion

The long half-life and high doses of human IgG4 therapeutics require an immunogenicity assay that is able to perform in high concentrations of the drug. The PandA and Bead methods provided the best signal-to-noise ratio. Since both the PandA and Bead methods provided the required minimum sensitivity and drug tolerance, they were further evaluated and shown to be free of drug interference as demonstrated by the absence of signal for the drug at 300 µg/mL.

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References


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