PPD® LABORATORIES CASE STUDY

Nitrosamines Analysis: Leveraging extensive experience, large testing capacity and leading-edge instrumentation

SUMMARY

PPD Laboratories' GMP lab utilized extensive experience, various technologies and high-quality scientific teams to develop and validate methods and complete testing on hundreds of batches of a large pharmaceutical company's drug product under tight timelines to identify N-nitrosodimethylamine (NDMA) as mandated by the U.S. Food and Drug Administration (FDA).

OBJECTIVE

Complete method development, validation and testing to screen and quantitate NDMA in a drug product with accelerated timelines to achieve regulatory timeline requirements.

BACKGROUND

N-nitrosamines are probable human carcinogens which must be measured and determined not to exceed very low levels. A series of events beginning in 2018 led to greater regulatory focus on N-nitrosamine contamination and resulted in a requirement for risk assessment and testing for N-nitrosamines in certain pre- and post-marketed products. In 2018, certain receptor antagonist/sartan drugs (e.g. hypertension and angiotensin II receptor blockers) were pulled from the market due to the detection of N-nitrosamines, including NDMA. This was followed by the detection of N-nitrosamines in certain ranitidine (antacid) and metformin (diabetes) drug products in 2019.

These events resulted in regulatory directives for pharmaceutical companies to perform risk assessments for the possible presence of N-nitrosamine compounds and to test all at-risk products.

A large pharmaceutical company approached PPD with the need to quickly develop and validate suitable test methods, then complete testing for hundreds of batches of a drug product to identify and quantify NDMA, addressing the industry-wide safety concern mandate from the FDA.

STRATEGY

Our GMP lab has more than 17 years of experience in the analysis of nitrosamines in pharmaceutical products, either as drug substance related impurities or as leachables produced in the container/closure systems.

17
years
nitrosamines testing experience

70
scientists and staff
completed analysis for hundreds of drug product batches

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To achieve method development, validation and testing for the large number of batches and meet the accelerated timeline, PPD Laboratories leveraged its extensive experience in nitrosamines analysis, including a wide variety of different genotoxic impurity methods. Our lab has worked with multiple pharmaceutical company clients in developing, validating, and batch testing for 10 different nitrosamines, including the most common nitrosamines such as N-NDMA, N-nitrosodiethylamine (NDEA), N-nitrosomethylethylamine (NMEA), N-Nitrosoisopropylethylamine(NIPEA), N-Nitrosodiisopropylamine(NDIPA), N-nitrosodi-n-butylamine (NDBA), N-nitrosomorpholine (NMOR) as well as N-Nitrosomethylphenylamine (NMPA), N-Nitroso-N-methyl-4-aminobutyric Acid (NMBA) and certain novel nitrosamines.

PPD Laboratories' GMP lab also leveraged access to leading-edge instrumentation to complete the task at hand. For this project, the first challenge in nitrosamine analyses is the extreme sensitivity requirement at the parts per billion (ppb) level; a second challenge was the highly complex drug product matrix. PPD Laboratories' GMP lab quickly surmounted these challenges through a combination of meticulous and creative sample preparation design and optimized GC/MS conditions. Our laboratory houses more than 10 GC/MS systems, which allowed the teams to complete method development, validation and testing that met an accelerated timeline required by the sponsor.

Following successful method validation, our extensive analytical team completed analysis for hundreds of drug product batches, including data review and issued dozens of reports in a short period of time. All tasks were efficiently completed while maintaining the highest quality standards, through a well-orchestrated team consisting of multiple analysts, project managers and quality assurance reviewers.

RESULTS

The majority of the batch test results were reported to be below the detection limit for NDMA, however, some batches did contain NDMA above the detection limit or reporting limit. Following the detection of NDMA above the reporting limit, an investigation was performed to confirm the results for these batches, including a verification using a high-resolution LC/MS method, which confirmed the presence of NDMA in the drug products and the amounts obtained from original GC/MS analysis. The batches with NDMA above detection or reporting limits were found to be related a specific manufacturing site with a unique manufacturing process.

Complete method validation, including the final validation report, was issued in two weeks; and 80 samples were tested within the first week. The study was successfully completed within the timeline, inclusive of the investigation and results verification work.

80
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