Helping Clinicians
Make Better Decisions

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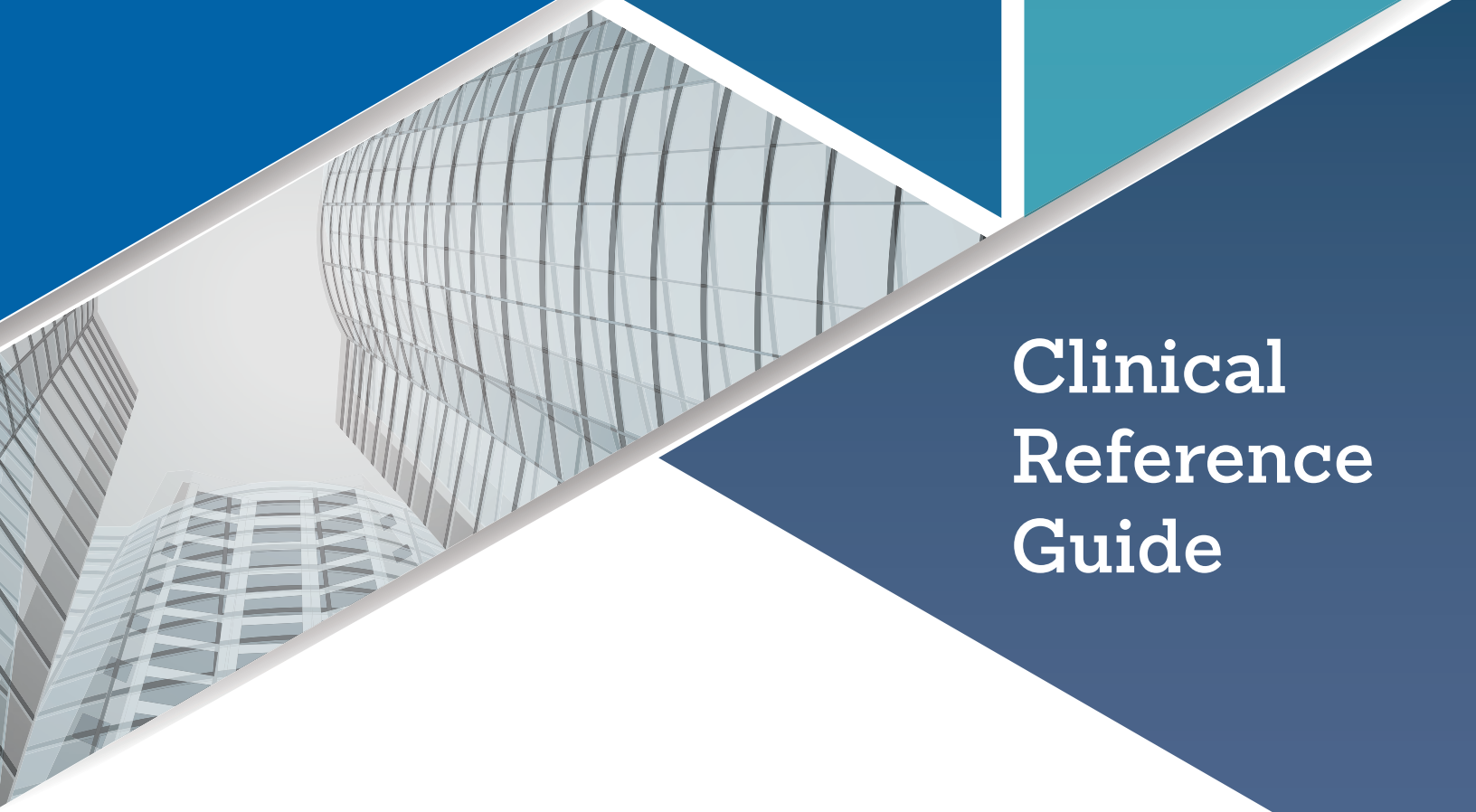

Clinical Reference Guide

Quality Assurance

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Aegis participates in voluntary laboratory accreditations and rigorous quality control to ensure accurate and reliable test results. The selection of a healthcare laboratory that does not have such quality resources in place may negatively impact patient care.

Not all definitive testing is of the same quality, even when performed using liquid chromatography/tandem mass spectrometry (LC/MS/MS) or gas chromatography/mass spectrometry (GC/MS). Poor instrument maintenance, lack of rigorous method validations, or foregoing the regular use of quality controls can impact the validity of results. There is no easy way for a clinician to ascertain the accuracy of a particular laboratory without first examining a laboratory's certifications and accreditations. Many laboratories do not seek voluntary accreditation by agencies that will subject them to rigorous proficiency testing programs and on-site inspections.

A. Laboratory Certifications and Accreditations

Aegis Sciences Corporation was founded in 1990 as a sports anti-doping and forensic reference laboratory. Many of the elements which ensure quality in forensic testing programs have been adapted to our testing in healthcare. Consequently, we are prepared to defend the accuracy of our results. The Aegis Quality Management System (QMS) exists to ensure that our methods are accurate and of the highest quality. All of our laboratories are subjected to the rigorous requirements of proficiency testing and on-site inspection to maintain laboratory certifications and accreditations. As a nationally recognized laboratory, we comply with a wide variety of regulatory requirements.

The process of certification and licensure by external regulatory organizations and the involvement in proficiency testing programs is critical to ensure quality of results, but is not required as part of the minimum standards for laboratories to perform testing. For example, a laboratory's participation in the College of American Pathologists (CAP) accreditation program is voluntary and demonstrates commitment to continuous improvement and a high standard of patient care. Additionally, accrediting organizations may require proficiency testing and alternative performance assessments to be conducted across all analytical testing methods to verify results are accurate and reliable.[1] Periodic on-site assessments are performed by these external agencies to ensure continued compliance to the program's requirements. Requesting information about a laboratory's certifications, accreditations, and engagements in proficiency testing programs is imperative to verify commitment to quality.

Laboratories in which healthcare testing is completed at Aegis undergo proficiency testing through the following organizations:

- College of American Pathologists
- Research Triangle Institute International
- Pennsylvania Department of Health

Organizations by which Aegis undergoes proficiency testing may change over time. An extensive list of up-to-date accreditations across all laboratories is available upon request.

B. Quality Controls

Aegis operates a stringent quality control program which involves routine instrument maintenance by a dedicated on-site team, extensive staff training and education, method validation, quality control samples analyzed with each specimen batch, and routine testing of parallel blind patient samples. Even with these safeguards in place, toxicology results undergo scientific review to verify that all quality control measures are met and the pre-analytical, analytical, and post-analytical systems function appropriately and as intended.

At Aegis, analytical batch data is reviewed by an expert certifying scientist. Our certifying scientists hold university degrees in the sciences and undergo intensive certification training before they are allowed to begin certifying toxicology results. Specific quality control criteria must be met before data will be certified; should any of these fail, specimens are sent back for re-analysis. This approach to data review, while adding

to the time needed to complete testing, is necessary to ensure quality reporting of data.

Aegis's Quality Team leads a robust and continual effort to improve process and performance. The interdisciplinary team works to continually investigate our systems and processes, including LC/MS/MS setup and design, software platforms, and typical processing steps; and to develop and implement new solutions to increase the precision and accuracy of our processes and associated results. Such an approach should be standard for any laboratory, particularly one performing high complexity mass spectrometry-based testing in healthcare.

C. Description of Testing Practices

Laboratories that offer medication adherence testing differ in regard to sample volume required for testing, testing methodologies employed, thresholds utilized, and average turn-around-time for results. Methods used to guarantee faster turn-around times are not always the most analytically accurate or consistent with good laboratory practices. Reduction in turn-around-time may be accomplished through reliance on presumptive testing results using immunoassay or even mass spectrometry to achieve faster report delivery. This approach raises concern for false positives and also increases the risk of false negatives.

Additionally, completion of testing for all analytes using a single LC/MS/MS analysis may allow for shortened turn-around-time. This practice may reduce the quality of results due to compromised conditions required by inclusion of drugs with vastly different chemical properties in one analysis. For example, although opiates and benzodiazepines can both be tested by LC/MS/MS, combining the two drug classes in one LC/MS/MS method would normally decrease the effective detection of the full range of compounds (especially opiate normetabolites).

Analytically, performing an analysis of all compounds in one LC/MS/MS analysis may result in the following:

- As resolution decreases and chromatographic peaks begin to overlap, the ability of the mass spectrometer to uniquely distinguish one analyte from another decreases.
- Peaks do not achieve a Gaussian (bell) shape but may begin to tail, possibly affecting the accuracy of the quantitation or the qualitative data as well.
- Compounds may not separate sufficiently and may escape detection altogether. Matrix varies from sample to sample, and interferences can cause false negative results.

Determination of testing methods employed (i.e., GC/MS, LC/MS/MS) should also be key when evaluating laboratory practices. In an attempt to hasten the reporting process, laboratories may elect to forego definitive testing of compounds that do not lend themselves to analysis via LC/MS/MS (e.g., barbiturates), instead choosing to report only immunoassay results for the drug class. Such procedures may increase the risk of false positives and false negatives.[2-4] Interpreting a toxicology report in these situations becomes a confusing enterprise. When both immunoassay and definitive testing technologies are used to report positive results, special care must be taken by the practitioner when interpreting results that may affect patient care. Furthermore, the argument that utilizing LC/MS/MS as opposed to GC/MS demonstrates superior testing capability is inconsistent with principles of analytical toxicology and is grounded more in marketing than actual science.

Although mass spectrometry testing is complex and can be time consuming, use of appropriate methods is imperative to ensure accuracy. Aegis has implemented state-of-the-art technology, and we continue to explore new options to streamline the process and provide timely results. Currently, we expect a turn-around-time of 96 hours or less once a specimen is received at the laboratory for healthcare testing.

Aegis uses strict criteria in our methods and reporting of data. All positive results are reported only after mass spectrometry definitive testing. While these many quality steps may increase our turn-around-time, it ensures the accuracy of our results. We are committed to employing the best technology that is available to optimize the quality and accuracy of our laboratory testing and reporting, while meeting realistic turn-around-time expectations. These strategies are intended to provide an effective and accurate analytical toxicology service

to help clinicians make better informed decisions regarding patient healthcare.

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