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Quality management in clinical application of mass spectrometry measurement systems

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ABSTRACT

Thanks to highly specific analyte detection and potentially complete compensation for matrix variables based on the principle of stable isotope derivative internal standardisation, mass spectrometry methods allow the development of diagnostic tests of outstanding analytical quality. However, these features *per se* do not guarantee reliability of tests. A wide range of factors can introduce analytical errors and inaccuracy due to the extreme complexity of the methods involved.
Furthermore, it can be expected that the application patterns of MS methods in diagnostic laboratories will change substantially during the coming years – with presumably less specialised laboratories implementing mass spectrometry. Introduction of highly automated test solutions by manufacturers will require some trade-off between operation convenience, sample throughput and analytical performance.
Structured and careful quality and risk management is therefore crucial to translate the analytical power of mass spectrometry into actionable and reliable results for individual patients' care and to maintain the degree of reliability that is expected from MS methods in clinical pathology. This reflection review discusses whether particular quality assurance tools have to be applied for MS-based diagnostic tests and whether these tools are different from those applied for optical- and affinity-based standard tests. Both pre-implementation strategies and surveillance of assays with assessment of metadata in routine testing are addressed. The release of the CLSI guideline C62-A in 2014 was a substantial achievement in this context because it addresses a wide spectrum of relevant issues in quality assurance of mass spectrometry-based clinical tests. However, the translation of this best practice document into individual laboratory settings is likely to be heterogeneous.

During recent years, an increasing general awareness of quality aspects in medicine can be observed. This phenomenon has been documented by the recently released Institute of Medicine (IOM) document" Improving Diagnosis in Health Care" [1,2], amongst other publications. However, only a short section of this report addresses diagnostic testing, and this section mainly focuses on "extra-analytical" elements of the total testing process. The IOM report concludes: "the contribution of the analytical phase to diagnostic errors is small". For many clinical pathologists, this very optimistic perception of analytics performed in clinical laboratories is somewhat surprising, especially when considering reports on adverse clinical outcomes, e.g., due to false-positive hCG results caused by heterophilic antibodies [3–5].

Though recent projects in clinical pathology address the quality of the analytical phase, this seems to be predominantly focused on statistical quality control approaches with estimation of measurement uncertainty observed when applying (e.g., commercially obtained) quality control samples with matrices often not related to the investigated body fluids. This is doubtlessly important for stable and safe handling of an analysis platform over time, but inaccuracy and gross errors occurring in individual analyses as a consequence of method inherent pitfalls – such as cross-reactivity patterns and anti-reagent antibodies in ligand binding assays, drug-mediated background signals in enzymatic assays, or matrix effects in MS applications – seem to remain largely neglected.

The introduction of MS into clinical chemistry has promised to minimise the risk of such issues significantly due to the very high specificity of detection. Indeed, most physicians have a favourable preconception of the analytical quality of this emerging technology. It is essential, though, to recognise that mass-spectrometric methods are extremely complex and are also prone to a variety of pitfalls that may lead to grossly inaccurate results [6] – requiring systematic quality management and sustained critical vigilance of mass spectrometry methods applied in the clinical laboratory.

According to ISO standard 9000, quality management can be defined as coordinated activities to direct and control processes with regard to quality or as the comprehensive policy of a laboratory to meet stated

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Table 1
Strong points of LC-MS/MS application for quality in the clinical laboratory.

Compensation of between-patient variables in matrix effects by stable isotope dilution internal standardisation
Highly specific detection of analyte based on orthogonal analytical principles (chromatographic retention, molecular mass, molecular fragmentation pattern, ion mobility)
Detection can be based on several mass transitions that are acquired simultaneously
Antibody-free and simple reagents (in terms of stability and cost)
Traceability directly to certified reference materials, no impact of cross-reaction patterns as with immunoassays
Reference ranges and decision levels independent from test antibodies
No impact of anti-reagent or anti-analyte antibodies

quality standards. The aim of this article is to discuss quality management aspects that are *particular* to MS methods applied in the clinical laboratory while incorporating our experience from >15 years of LC-MS/MS application in a clinical laboratory.

1. The role of mass spectrometry in the clinical laboratory today

It is a widely accepted view that quantitative mass-spectrometric technologies have the potential to become a third mainstay of clinical chemistry besides photometry and immunoassays [7–13]. This is mainly because new mass-spectrometric technologies enable the development of straightforward and extremely flexible methods and also allow highly parallel quantification of a wide spectrum of low- and high-molecular weight analytes, irrespective of specific molecular features for detection (such as UV absorption or thermal stability). On the other hand, mass-spectrometric applications (assay plus instrument) show a far higher level of complexity compared to photometry and immunoassays. It is still not entirely clear if this high level of complexity will be compatible with large-scale application of quantitative mass spectrometry as a standard technology in regular clinical pathology laboratories.

Today the proportion of MS-based analyses among the total number of tests performed in clinical chemistry worldwide is still very small – but increasing. MS is applied in highly centralised new-born screening laboratories in most industrialised countries. Hence, every citizen will at least once be exposed to MS as "customer" now. It is also used in specialised laboratories of tertiary care and teaching hospitals and in some centralised private laboratories, with high disparities between nations. The technique is predominantly applied for testing in TDM, clinical toxicology, for few endocrine parameters, and for some metabolic investigations (such as methylmalonic acid). The majority of assays are still "laboratory-developed tests" (LDT), while commercially available kit solutions are increasingly used. Although basically technically amenable, protein analyses using MS are performed in only a small number of highly specialised laboratories worldwide.

2. MS - opportunities and threats for quality

Mass spectrometry – in particular tandem-mass spectrometry – boasts a set of features that offer excellent prerequisites to for diagnostic tests of highest analytical performance and reliability (see Table 1).

On the other hand, it must also be noticed that several general features of this technology can threaten quality and patient safety when not adequately addressed (Table 2). In particular, the complex interplays of a number of orthogonal processes and variables, such as the multistep process of sample preparation, (chromatographic) pre-fractionation, ionisation, ion-manipulation, signal readout and evaluation. Mass spectrometry relies on delicate interaction between processes of biochemistry, gas-phase chemistry, physics, electronics, and data handling. A major challenge for quality management is the enormous heterogeneity and poor standardisation of instrument configurations and procedures [14]; there are indeed hardly two completely identical LC-MS/MS systems in a clinical laboratory. The process of signal generation is rather inconstant, due to, e.g., pulsation of the electrospray and contamination/charging of ion optical components. This is in strong contrast to optical- and affinity-based clinical chemistry analyser systems; actually, a LC-MS/MS system resembles to some degree a "living system" interacting with and reacting to its environment (e.g., changes in room temperature).

In addition to these general issues, a variety of more specific pitfalls may cause inaccurate and false results (Table 3). It must be assumed that this list is not comprehensive, and – due to the multi-dimensional complexity of methods – it seems warranted to be generally vigilant of yet unidentified sources of failure. Clinical mass spectrometry assays should be the subject of sustained analytical research and risk management. We must address i) how substantial the risk of inaccurate results related to recognised issues is, ii) how frequently such issues may occur, and iii) how likely the detection of failures related to an issue is.

3. Good tests, bad tests

It has to be emphasised that for many analytes, the application of mass spectrometry allows the development of highly reliable test - but that application of this technology does not guarantee safe methods. Currently mass spectrometry requires significant analytical expertise to develop *and* to maintain tests that are fit for diagnostic purposes. Unfortunately, some instrument vendors like to suggest a different picture. Although formally employing stable isotope-based internal methods, clinical MS/MS analytical methods can indeed be of insufficient reliability. Table 4 gives putative examples of a very reliable method and of a method with substantial risk of generating inaccurate results and potentially leading to patient harm.

4. Trajectory of quality in clinical mass spectrometry

Compared to standard clinical chemistry analysis systems based on conventional technologies and already made quite safe in operation

Table 2
General issues potentially compromising the quality of MS methods applied in the clinical laboratory.

Heterogeneity of instrument configurations (multiple manufacturers, multiple instrument configurations of both MS analysers and chromatography modules)
Inconstant nature of signal generation in atmospheric pressure ionisation (variance of ion yield in the short term (e.g., pulsation of the electrospray), middle term (e.g., charging of parts of the ion optics) and longer term (e.g., contamination of ion source and ion optics)
Substantial differences in the performance observed even between identical instruments (in contrast to standard instruments in the clinical laboratory)
Individual tuning of instruments, in-complete options of documentation (e.g., position of the source probe)
Individual development and/or implementation of methods necessary, requiring substantial expertise and skill of operators (also in the case of kits)
Complex instrument software that further addressing the needs of a research laboratory than of a high-throughput diagnostic laboratory
Very complex instrument handling compared to standard clinical chemistry analyser systems
Extensive training of technicians required for safe operation
Lack of automation; typically, extensive manual handling with substantial risk of gross errors in most assays