Fuelling a new era of innovation in mass spectrometry

cobas® Mass Spec

November 2023

Table of contents

Chapter 1
The challenge: mass spectrometry today

The medical and clinical need for mass spectrometry has been present for a long time.

From 2008 to 2018, the number of publications related to mass spectrometry tripled[1] and a consistent increase of samples tested using mass spec has been reported in literature for several years.[2-4]

The main reason behind this shift is that there are limitations in standard testing methods like immunochemistry and clinical chemistry. For specific patient cohorts, liquid chromatography combined with tandem mass spectrometry (LC-MS/MS) provides better analytical sensitivity, better specificity and/ or accuracy, whilst being less impacted by matrix effects, interferences or cross-reactivity.[5]

LC-MS/MS has consequently become a widely used technology within clinical reference and referral laboratories world-wide and has also started to be used in some hospitals and regional clinical laboratories.[4]

Mass spec is well established in clinical and academic research and is also used predominantly in the following fields: therapeutic drug monitoring (TDM), drugs of abuse testing (DAT), newborn screening, endocrinology, small molecules, vitamins, peptides and protein markers. Mass spec technology is well-known for complex and sophisticated reference methods. Overall, mass spec today is found in separated, specialised testing sections of the laboratories, but there are hurdles that prevent more labs from adopting mass spectrometry in routine operation. Two of the main challenges are that the process can be time-consuming and requires high levels of expertise to be carried out successfully.

Typical weaknesses of existing mass spec solutions were previously described by Vogeser & Zhang in 2018.[5]

- High complexity of instrumentation
- Hardware & software are designed for highly specialised research labs, but not for clinical routine diagnostics
- Lack of automated solutions from sample preparation to sample analysis to result reporting
- Poor integration of mass spec with laboratory information systems
- Operation and troubleshooting of instrumentation requiring highly skilled staff
- Poor standardisation across instruments and even more assays across laboratories
- Long turnaround times which are not suitable for urgent care
- Complex data handling

There are limitations in standard testing methods like immunochemistry and clinical chemistry

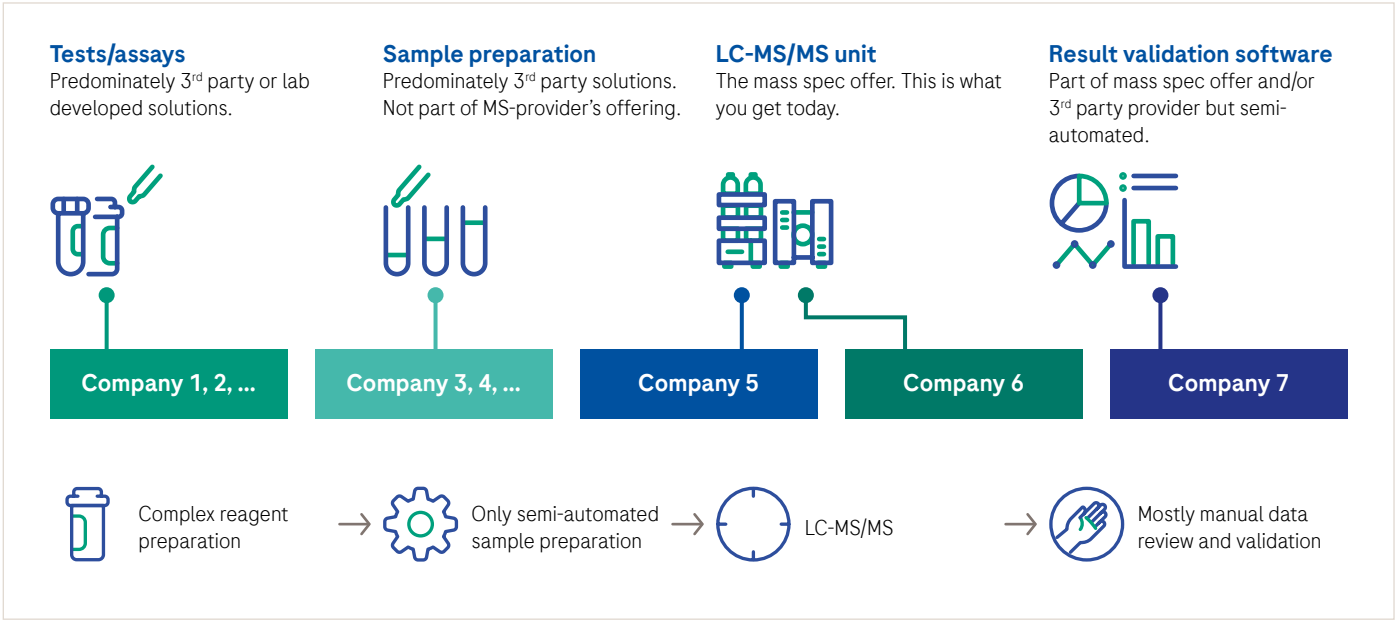
One of the main weaknesses, the long turn around time, is due to the typically required batch mode. For more complex analytes, long separation procedures using liquid chromatography allow only a small number of samples to be processed. Furthermore, there are no routine-suitable service concepts in place in the event of technical problems.

Due to the lack of a total solution provider, laboratories typically need to interact with numerous different companies to obtain everything required for mass spec. In the most complex cases, labs are required to deal with up to 7 vendors to provide all the necessary materials and services, seen in Figure 1.

Different vendors may need to be engaged to deal with the following:

- Commercially available reagents for calibrators & quality control (QC) or reference material for in-house preparation of calibrator and QC material
- Reagents and consumables for sample preparation and mobile phase of the LC system
- Semi-automated sample preparation solutions
- Instrumentation for liquid chromatography (LC) & mass spectrometry (MS), typically sourced from the same provider
- Software solutions for semi-automated result interpretation and validation

Figure 1: A key challenge for mass spec testing today is the lack of a total solution provider



Chapter 2
The vision: the future of mass spectrometry

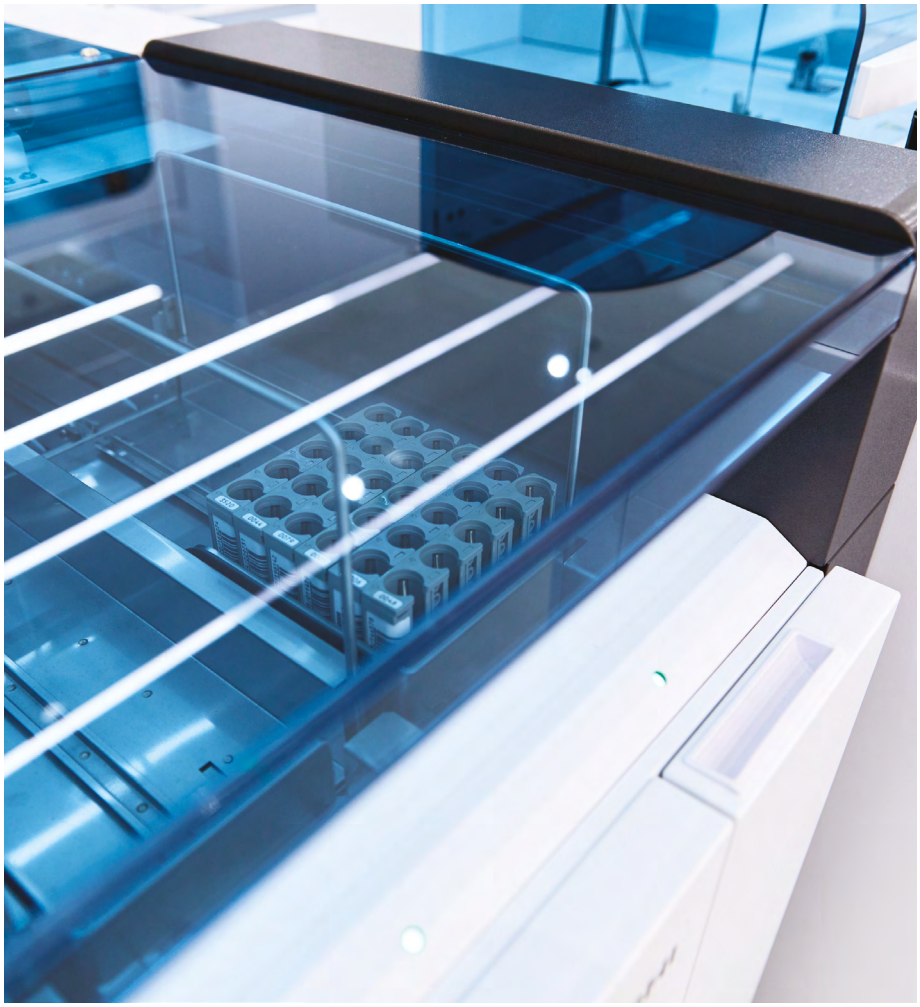
The vision for the future of mass spec solutions is clear and has been outlined in publications for many years. In 2015, Zhang & Rockwood had the vision of developing mass spectrometry into “a total automation, high throughput, continuous random-access platform.”

The authors envisioned that an “automated mass spectrometry platform can in the future either be a standalone floor model or integrated into the core laboratory function as one of the automated platform along with chemistry analysers, haematology analysers, coagulation analysers and others.”[6]

Stone & Fitzgerald further specified this vision of future clinical mass spectrometry in 2018: “Such a system would have ease of use similar to automated clinical chemistry analysers – random-access workflow, minimal down-time, 24/7 service and support, and validated and ready-to-use reagents and calibrators supplied by the vendor. These systems would not require specialised end-user skills for operation and would have sampling and software that permit integration to track systems along with ASTM/HL7 interfaces to laboratory information systems.”[7]

As a logical consequence of the envisioned automated solutions which would be integrated into routine laboratory track systems, Greaves et al. predicted in 2019 that there would be an increase in the number of clinical laboratories adopting mass spectrometry based testing, especially in the fields of endocrinology and drug testing.[1]

Zhang & Rockwood had the vision of developing mass spectrometry into “a total automation, high throughput, continuous random-access platform.”



Chapter 3
The answer: Roche vision of cobas® Mass Spec

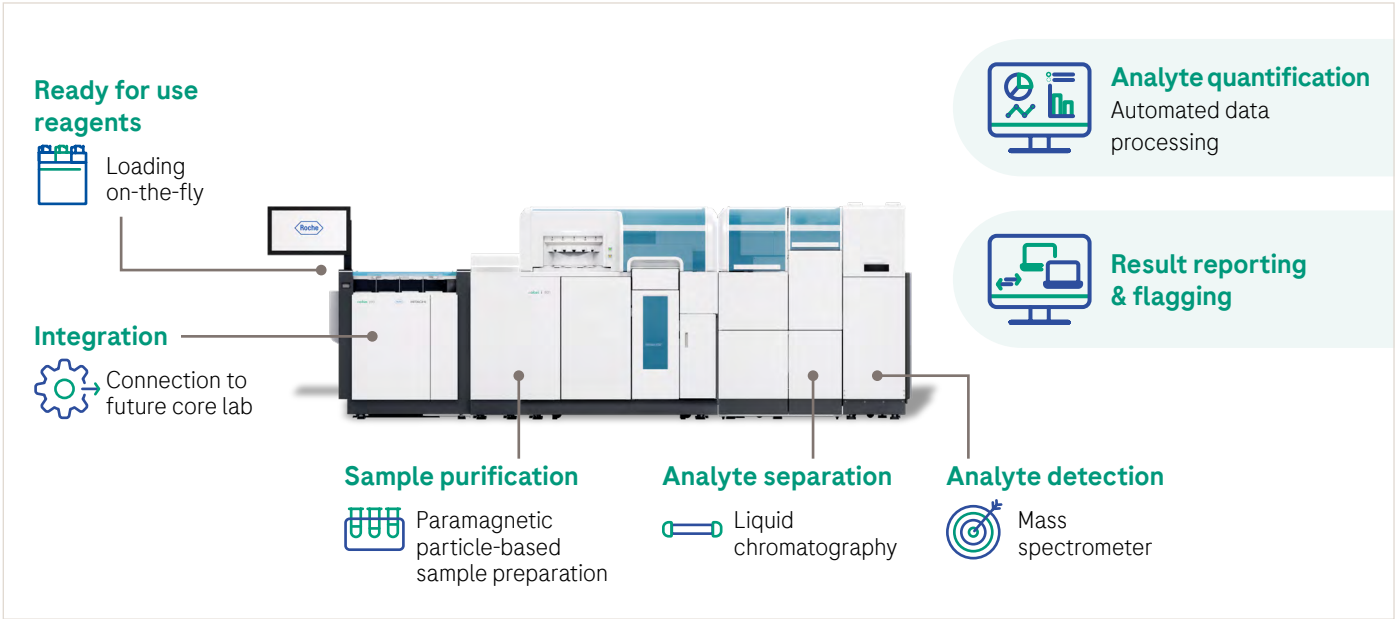
The aforementioned visions will be made a reality by the **cobas**® Mass Spec solution. Roche Diagnostics is investing in developing a solution for clinical mass spec testing, which is destined to be compliant with IVD regulations, addressing unmet needs and providing answers to the current challenges faced by clinical mass spec operations:

- **Full automation** from sample preparation to result interpretation with random access operation mode
- **Seamless integration** into the clinical chemistry, immunoassay testing and beyond via **cobas**® **pro** integrated solutions
- **A high throughput** of up to 100 tests/ hour to fit the needs of the core laboratory for fast and predictable turnaround times
- **A broad assay menu** of over 60 analytes planned in two staggered launch waves consolidated on a single platform

The **cobas**® Mass Spec analyser, which will be called the **cobas**® i 601 analytical unit, is designed to transform a complex technology into an integral part of clinical routine testing. It is designed to be a total solution from sample to result for clinical mass spec testing and will include the following, as seen in Figure 2*:

- Ready-to-use reagent cassettes with the same design as the well-received **cobas**® c and **cobas**® e reagent packs
- An automated paramagnetic particle-based sample preparation, ensuring efficient sample purification
- Fully automated liquid chromatography and mass spectrometry with a **cobas**® look and feel
- Fully automated data processing, automated result reporting and result flagging to replace manual analyte quantification
- Integration into **cobas**® **pro** integrated solutions to provide connection to the central laboratory

Figure 2: cobas® Mass Spec solution, a sample-to-result total solution for clinical mass spec testing



cobas® Mass Spec solution (including **cobas**® i 601 analytical unit and Ionify® reagents line) is in development, not approved by regulatory bodies, and not commercially available. Intended product specifications, information and timelines are design goals and might be subject to change. All statements relate to the product after launch.

Chapter 4
The future: cobas® Mass Spec

Here are a few examples of how **cobas®** Mass Spec intends to provide clinical laboratories with a number of benefits:

Fully automated mass spec testing can help to increase efficiency in the laboratory workflow and reduce human errors

cobas® Mass Spec will provide a fully-automated solution from sample preparation to result reporting. After preparing the system, the only action for a lab operator is to load the samples into the analyser. The system will automatically conduct sample preparation, separation and detection, validating the results and finally transferring to the laboratory information system (LIS).

As demonstrated in Figure 3, this will reduce the potential for human error, as well as hands-on time, which in turn will allow the overall efficiency of the testing workflow to be improved.[6]

Convenient and simplified reagent handling can free up staff time

In current mass spec offerings, reagent preparation can be a complex process. Reagents are typically not ready to use (e.g. internal standards and mobile phases need to be prepared). Additionally, appropriate chemistry knowledge and a suitable laboratory is required. With **cobas®** Mass Spec, a streamlined reagent concept will be offered, which will allow fast and easy handling. This will free up time for laboratory staff and will minimise the risk of human error. Product-specific reagents, as well as multianalyte reagents will be provided in easy-to-handle reagent packs or containers, as illustrated in Figure 4*.

Figure 4: Reagent handling process will be simplified and more convenient

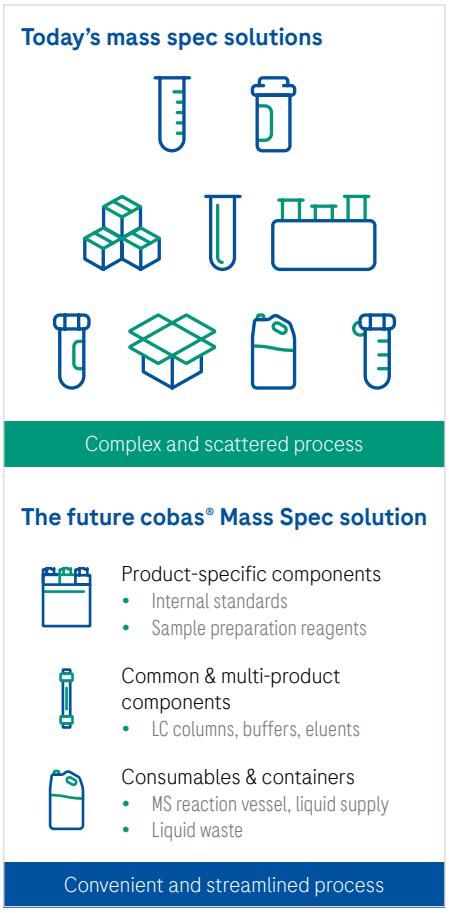
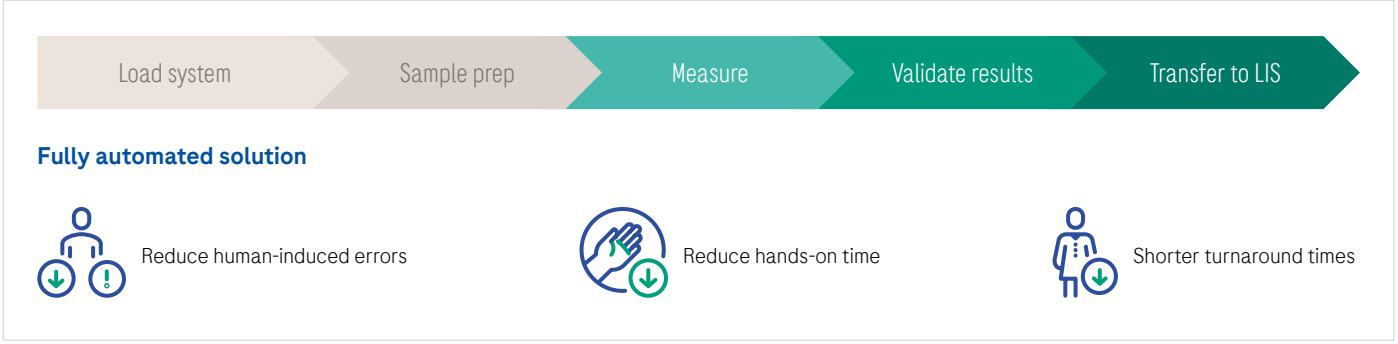


Figure 3: Fully automated mass spec testing allows to safe time and resources



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A fully automated IVD solution saves validation efforts

Currently, to develop and validate LC-MS/MS based methods, a number of different steps need to be considered, and guidelines have to be followed to validate them. These are time-consuming and require high expertise, which can add strain to lab staff.[8,9]

cobas® Mass Spec is destined to be a solution compliant with IVD regulations, covering the workflow as a whole

cobas® Mass Spec is destined to be a solution compliant with IVD regulations, covering the workflow as a whole, including the instrumentation, software and reagents. Performance data will be provided in assay method sheets, based on many internal experiments, as well as internal and external validation and verification data. Mass spec experts will be relieved from the cumbersome test development process and can focus on more esoteric methods or methods used in fast-changing environments like drug of abuse testing.

With a random access analyser patient results can be provided earlier

With **cobas**® Mass Spec, random access will be introduced to the world of mass spec testing. Traditionally, users need to change the instrument condition, exchange reagents and columns to run a specific application. When switching to another application, the system has to be re-engineered. This means that the system is currently limited to batch-mode testing which is time-consuming and inefficient.[10]

With **cobas**® Mass Spec, random access will be introduced to the world of mass spec testing

cobas® Mass Spec will allow loading and processing samples as they arrive in the laboratory. No batch mode testing will be required, which will allow both the efficiency and flexibility of the process to increase and this in turn will allow earlier release of patient results.

Automated result validation and reporting simplifies processes

In the current offering in the market, reviewing and releasing results does not only require high expertise but it is also labour-intensive.[6]

cobas® Mass Spec will introduce a sophisticated algorithm to automatically process the data

cobas® Mass Spec will introduce a sophisticated algorithm to automatically process the data generated from the mass spectrometer. Data will be processed, validated and calculated, and results will be reported directly without visually controlling every single peak. In the case of a flagged result, there will be an alert which signals that the result needs to be reviewed before sending it to the LIS.

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A broad variety of analytes in the launch menu will increase the accessibility to mass spec in clinical routine testing

As illustrated in Figure 5*, assays for more than 60 analytes are in development and will be launched in two staggered waves. The first wave comprises steroids, vitamin D and regular-tested TDM parameters, including the full portfolio of whole-blood based immunosuppressant drugs. The assays will be provided in 14 ready for use multi-reagent packs.

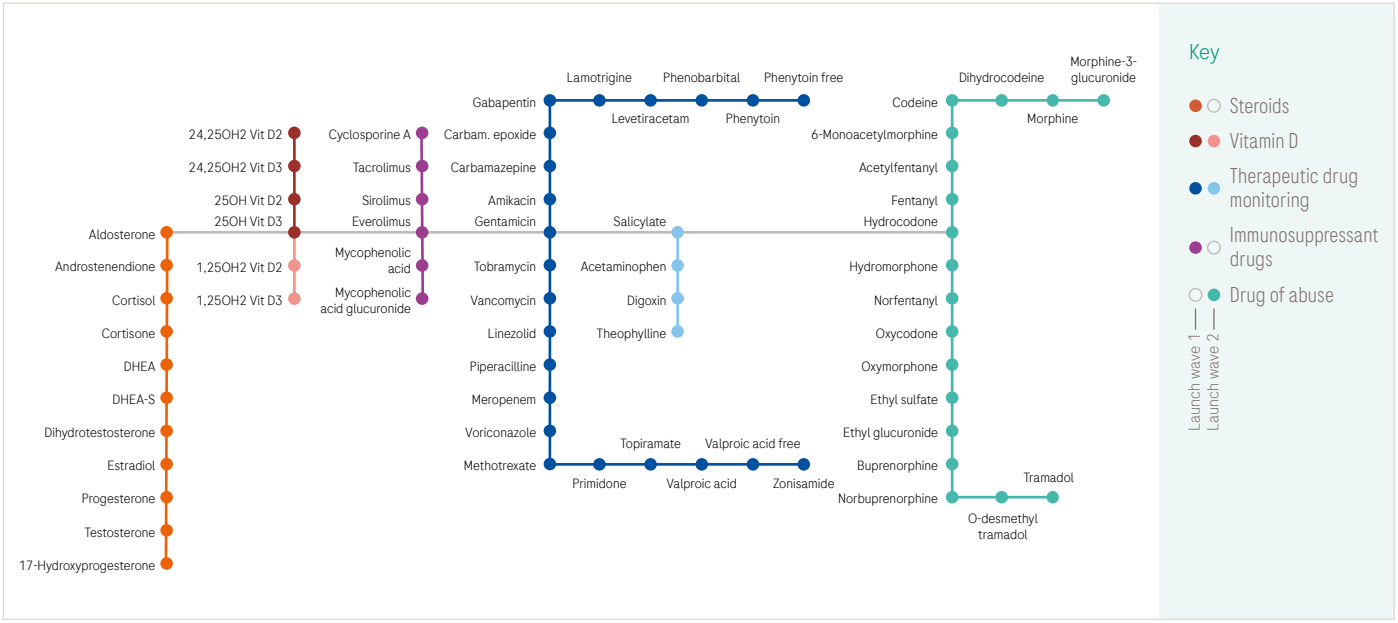
Standardised and traceable methods are prerequisites for consistent patient results

Another challenge in today's mass spec world is the lack of standardisation, which is even more prevalent in clinical mass spec testing. Laboratory developed tests (LDTs) are mainly used in current clinical mass spec testing procedures. The lack of total solution providers has as consequence, that there are numerous instrument configurations, different pre-analytic and analytical methods, various data acquisition conditions, calibration and quality control concepts, and finally, methods to interpret results.

This means that it is difficult to compare the results between the labs and even between instruments. Furthermore, there is in general a lack of standardisation due to the lack of suitable reference measurement procedures or reference materials.[9,11]

Roche Diagnostics is developing standardised reference methods by collaborating with external mass spec experts. All assays included in the **cobas**® Mass Spec launch wave 1 will be traceable to reference methods, which allows standardisation of mass spec testing. This in combination with **cobas**® Mass Spec, which includes all process steps required from sample to result, ensures that results can be compared with other labs using the same solution.

Figure 5: cobas® Mass Spec assay menu provided in launch wave 1 (solid colours) and launch wave 2 (light / pastel colours), with each colour representing a different indication or drug class.



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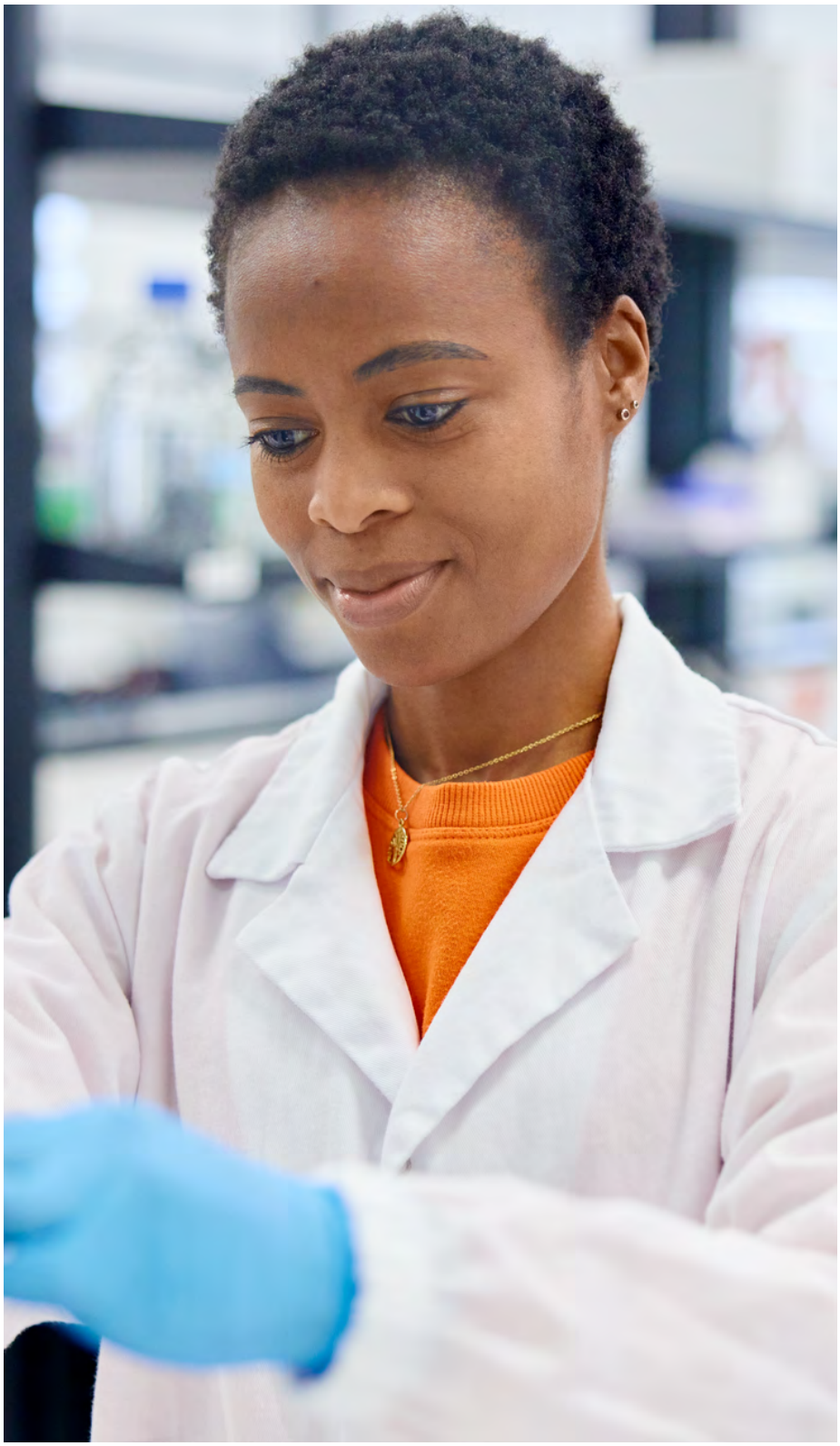
Simplifying calibration concept

The current standard of clinical mass spec LDT is characterised by batch mode analysis and typically 6 to 8 calibrator levels included at least once, if not several times per batch. This results in a significant number of calibrators which need to be prepared or thawed and tested with every batch run.

The proposed traceability concept allows a simple calibration of **cobas**® Mass Spec applications. The **cobas**® Mass Spec calibration follows the concept established in today's immunoassay solutions. Instead of calibration with 6 to 8 calibrator levels, a 2-level re-calibration of a prefabricated calibration (or factory calibration) curve will be applied. Intensive testing done at Roche will significantly increase calibration robustness and lead to a clearly longer calibration interval.

More than **60 analytes** are in development



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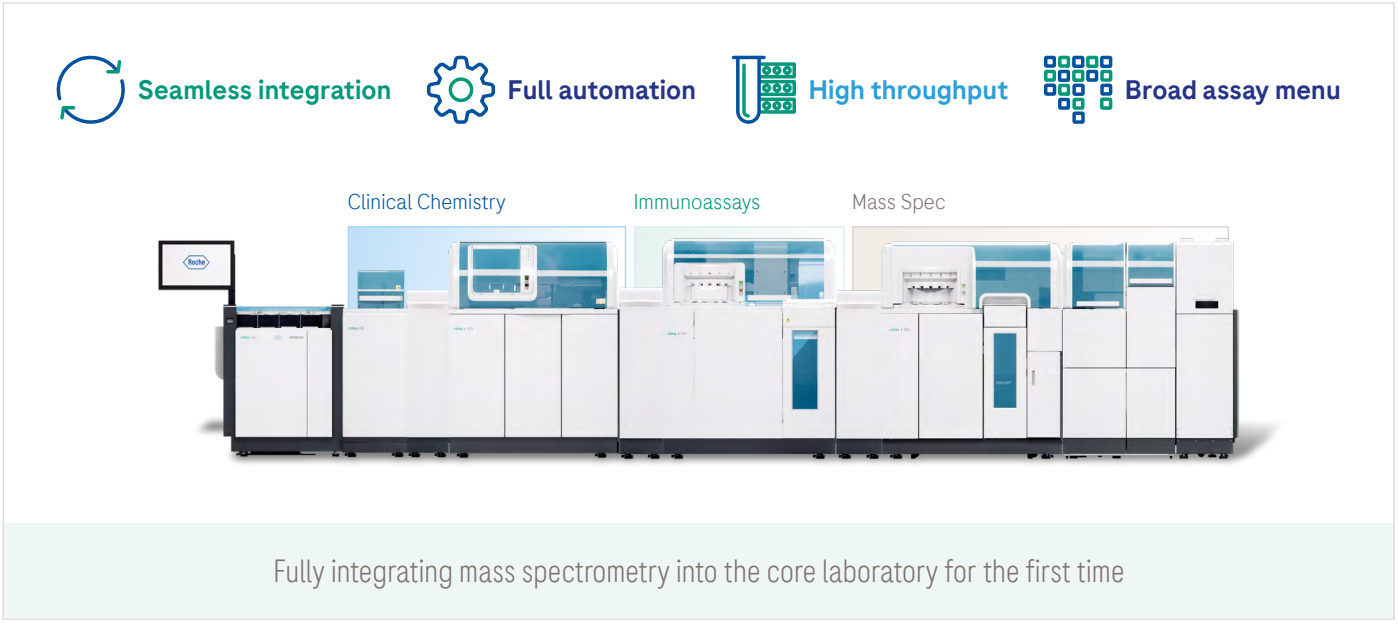
Chapter 5
Summary

In summary, the three main hurdles for the laboratories to adopt mass spec as a technology in core laboratories are the high operational complexity, the lack of automation, standardisation and integration and also the need for skilled operating staff.

The design goal of **cobas**® Mass Spec is to fully automate the mass spec testing and make it as easy to use as current clinical chemistry or immunochemistry testing. The design of the solution fulfils requirements in routine clinical setting like throughput and random access testing, and allows to seamlessly integrate mass spec testing into the core lab which can be seen in Figure 6*.

Figure 6: The future of mass spectrometry



Fully integrating mass spectrometry into the core laboratory for the first time

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