Review

Laboratory testing in pharmacies

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Abstract

Point-of-care testing (POCT) is traditionally defined as laboratory diagnostics performed at or near the site where clinical care is delivered. POCT thereby combines sample collection, analysis, and reporting of results into a robust integrated testing structure, with a simple user interface. The availability of reliable devices and consolidated tests for patient screening, diagnosis and monitoring has allowed broad diffusion of POCT to the patient’s bedside, physician offices, pharmacies, other healthcare facilities, supermarkets, and even into the patient’s home. However, current evidence clearly shows that POCT can be subjective, and might even amplify the traditional problems encountered in the preanalytical, analytical and postanalytical phases of the total testing process. This may especially be seen in inappropriate test request, collection of unsuitable biological materials, inaccurate test performances, larger analytical imprecision, unsuitable report formatting, delayed reporting of critical value, and report recording/retrieval. POCT patient care service in the pharmacy can be regarded as a valuable option for the present and future since it might be beneficial for all parties. However, several economic, clinical and regulatory issues should also be addressed before this opportunity can turn into a real advantage for patients and the entire healthcare system. The most appropriate allocation of POCT within the diagnostic pathway, as well as its adjuvant role in screening, diagnosis and monitoring of diseases should also be clearly established in order to prevent widespread and deregulated implementation.

Keywords: pharmacy; point-of-care testing; waived testing.

Introduction

Laboratory diagnostics has undergone radical changes within the last century. Some of these changes have occurred within the network of hospital laboratories, while others involve the patient’s bedside, physician offices, pharmacies, and other healthcare facilities, supermarkets and even the patient’s home. Basically, remarkable advances in microchemistry (i.e., biosensors and whole-blood analysis), microcomputerization, miniaturization, and non-invasive testing procedures have permitted the production and marketing of small, hand-held devices which have substantially increased the use of in vitro diagnostics (IVDs) outside the laboratory setting. In this thriving scenario, the Clinical Laboratory Improvement Amendments of 1988 (CLIA 1988) has institutionalised this category of ‘simple’ diagnostics, which is now referred to as ‘waived’ testing (1). CLIA waived tests are thereby portrayed as tests or procedures that “are cleared by the United States Food and Drug Administration (FDA) for home use; employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible, or pose no reasonable risk or harm to the patient if the test if performed incorrectly” (2) (Table 1).

Point-of-care testing (POCT) is traditionally defined as “laboratory diagnostics performed at or near the site where clinical care is delivered”, which combines sample collection, analysis, and reporting of results into a robust integrated testing structure, with a simple user interface. POCT can also be categorized into two groups. One group includes equipment designed to be operated by a patient and the other includes equipment designed to be operated by a healthcare provider outside the confines of the laboratory. A more restrictive and comprehensive definition is provided by the College of American Pathologists (CAP): “…analytical patient testing activities provided within the institution, but performed outside the physical facilities of the clinical laboratories. It does not require permanent dedicated space, but instead includes kits and instruments, which are either hand carried or transported to the vicinity of the patient for immediate testing at that site”. There are two general platform types that support POCT: small bench-top analyzers, and hand-held devices. Therefore, the CAP definition currently fails to recognize devices used by patients for home care, or by caregivers or healthcare professionals, such as pharmacists outside of a hospital or similar healthcare facility.

More than 100 companies that market rapid tests exist worldwide and nearly one-third of the entire IVD testing market is now comprised of POCT. However, the market is
• Bedside testing: any evaluation of analytes close to a patient who may be in a relatively critical state.
• Bias: quantitative estimation of systematic analytical variation (e.g., difference between the actual measurement and the true value), that is usually expressed as percent deviation.
• CLIA 1988: The Clinical Laboratory Improvement Amendments of 1988 establishes quality standards for laboratory testing and an accreditation program for clinical laboratories. They vary according to the technical complexity in the testing process and risk of harm in reporting erroneous results. The regulations established three categories of testing on the basis of the complexity of the testing methodology, including waived tests, tests of moderate complexity, and tests of high complexity.
• Imprecision: quantitative estimation of random analytical variation (e.g., closeness of agreement between independent results of measurements obtained under stipulated conditions), that can be expressed quantitatively as a statistic: coefficient of variation (CV) = standard deviation (SD)/mean × 100.
• In vitro diagnostic medical device: any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body.
• In vitro diagnostic products: reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.
• Near-patient testing: tests performed in a few minutes, without the need for complex instruments or equipment.
• Pharmacy: (from the Greek φάρμακον 'pharmakon' = drug) the health profession that links the health sciences with the chemical sciences, and is charged with ensuring the safe and effective use of medication.
• Pharmacists: the experts on drug therapy and the primary health professionals who optimize medication use to provide patients with positive health outcomes.
• Point-of-care testing (POCT): diagnostic testing at or near the site of patient care.
• Total testing process: series of activities or path of workflow for performing testing that can be divided into three major phases: before testing (preanalytical), during testing (analytical), and after testing (postanalytical).
• Waived tests: simple laboratory examinations and procedures that are cleared by the Food and Drug Administration (FDA) for home use, employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible, or pose no reasonable risk of harm to the patient if the test is performed incorrectly.

Predicted to grow exponentially, such that it is projected to be $10 billion by the end of 2010 (3) and $18.7 billion by 2011. In 2008, 122,000 labs and 55,000 physician office labs in the US were already granted a Certificate of Waiver (CW) under CLIA. The primary care needs that support the introduction of POCT are basically to improve: (a) quality of care, (b) health outcomes, and (c) the financial feasibility of such practices (4). Therefore, besides consolidated tests for patient screening (fetal occult blood and urine dipstick chemistries testing; fertility/pregnancy; substance abuse), diagnosing (D-dimer, biochemical markers of myocardial damage) and monitoring [prothrombin time (PT), glucose, glycated hemoglobin, ketones, cholesterol, triglycerides], a variety of technological innovations (electronics, developments in Wi-Fi and graphical interfaces, spin-offs from bio-warfare testing, microtechnology, nanotechnology, integrated polymerase chain reaction devices) are paving the way for expanding the market to other pathologies (e.g., infectious pathologies), and for creating multi-assay platforms for concurrent testing of various diseases. However, a common drawback to rapidly changing, developing and improving technologies is the difficulty of maintaining a high level of efficiency and quality with minimal errors. POCT is no exception to this rule, since new platforms and applications continue to become available, and more facilities are adopting this practice. Pharmacists have traditionally spent most of their time in the pharmacy, but nowadays more are working in patient care units or at the “point-of-care.” (5). Using POCT, pharmacists might have a positive impact on healthcare in a variety of ways, including identification of patients at risk who might be referred to the next level of care for possible diagnosis and treatment, enhancement of continuity of care by providing patient data on the progression of a chronic disease between physician visits, involvement of patients in their own care by celebrating successes, and addressing therapeutic issues with the patient at the time when the patient receives the laboratory test results, design of disease management programs around a POCT device (e.g., diabetes management program using a glycosylated hemoglobin monitor or a cholesterol management program integrating a cholesterol monitor), identification of unnecessary or inappropriate medication or lifestyle therapies, increased revenue through billing techniques including fee for-service, capitation, or reimbursement contracts with self-insured employers (6). However, given the growing diffusion of waived testing in this healthcare environment, common deficiencies in POCT use may arise. Thousands of incidents, including a number of deaths, have already been registered with the US Federal Drug Administration during the past two decades, especially with use of glucose meters, which have the longest history and the widest use among POCT devices, despite also being one of the medical devices with the greatest number of complaints (7).

Overview on some national and international regulations

All facilities in the US that perform laboratory testing on human specimens for health assessment or the diagnosis, pre-
vention, or treatment of disease are regulated under CLIA. The CLIA of 1988 (CLIA 1988) laws specified that laboratory requirements be based on the complexity of the test performed, and established provisions for categorizing a test as waived. Tests may be waived from regulatory oversight if they meet certain requirements established by the statute (8). In 1992, regulations were published to implement CLIA waived tests, which were defined as simple laboratory examinations and procedures that are cleared by the FDA for home use, employ methodologies that are so simple and accurate as to render the likelihood of erroneous results negligible, or pose no reasonable risk of harm to the patient if the test is performed incorrectly. These regulations also mandate that all clinical laboratories, regardless of location or size (thereby including POCT), be certified by the Secretary of Health and Human Services. The Centers for Medicare and Medicaid Services (CMS) administers the CLIA laboratory certification program for the Secretary of Health and Human Services in conjunction with the Centers for Disease Control and Prevention (CDC) and the FDA. In particular, laboratories that perform waived testing must meet specific requirements, including enrolment in the CLIA program, payment of applicable certificate fees biennially, adherence to manufacturer’s test instructions, accomplishment of CW, and permission to be inspected by the Department of Health and Human Services (HHS) (9). In November 1997, the CLIA waiver provisions were also revised by Congress so that tests approved by the FDA for home use automatically qualify for CLIA waiver. Although professional use versions of home use tests are not automatically waived, they still qualify for expedited waiver review since only the differences between the home use and professional use versions need to be examined to determine whether the professional version qualifies for waiver. Under the current process, waiver may be granted to: (i) any test listed in the regulation, (ii) any test system for which the manufacturer or producer applies for waiver if that test meets the statutory criteria and the manufacturer provides scientifically valid data verifying that the waiver criteria have been met, and (iii) test systems cleared by the FDA for home use. CLSI recommendations include indications for conducting quality waived testing, introducing waived testing, good laboratory practices for the three phases of testing (see below), and continued monitoring of testing with a focus on personnel education and training. According to the FDA, a quality system provides a basic framework for laboratories and other healthcare units to direct and control activities and functions along the path of workflow, with a focus on managing quality. Accordingly, a specific Path of Workflow for Home Testing is identified, including preanalytical (e.g., obtain test, read instructions, set up test area, collect specimen), analytical (perform test, read result) and postanalytical (interpret result, obtain follow-up testing and counseling, as needed) issues (10).

In 1998, the European IVDs Medical Devices Directive (98/79/EC) was published and subsequently transposed into UK law under the Consumer Protection Act (Medical Device Regulations 2002). Accordingly, beginning the 7 December 2003, all products placed on the market in both the European Union (EU) and the European Economic Area (EEA) have to comply with the directive and local member state laws. The purpose of the IVD directive is to facilitate a single market with minimal technical barriers to trade. It provides harmonizing rules on the safety, quality and performance of IVDs, and sets out a common regulatory environment for IVDs across Europe. For these systems to work, the directive must first be transposed into national law; all member states should have a national version of the directive. Government Agencies known as Competent Authorities are responsible for the requirements of the Directive being followed. Products must be registered with a Competent Authority before they can be sold in the EU. The European Community (EC) mark is applied to the product by the manufacturer before it is placed on the European market. The CE mark may only be applied to a device for which the manufacturer has signed a declaration of conformity, indicating that it conforms to the requirements of the directive. The British In Vitro Diagnostics Association (BIVDA) is the national trade association for companies with major involvement and interest in the IVD industry. BIVDA represents both manufacturers and distributors who are active in the UK (11). The BIVDA has issued specific directive and regulations governing the sale of IVDs in the UK. In 2001, only France, Germany and Portugal had a formal process for registering certain types of IVDs. However, the national systems are different, resulting in the anomalous situation of a particular serological test being authorized in one country, but not in another. In France, the laboratory director has responsibility for all testing, irrespective of the location in the hospital where it is performed. This currently relates mainly to the maintenance, calibration, and operator training for the POCT devices (12). In several other countries, including Italy, there is no official legislation concerning POCT, and even within the same country, the regulation might differ widely from one region to another (e.g., in Italy, the regulations of Lombardy differs substantially from that of Tuscany).

In Australia, the IVD market is regulated by the Therapeutic Goods Administration (TGA), and this organization has recently released a working document on this subject (13). The TGA is grappling with the array of medical devices being developed and planned for release, including those for ‘home use’. The TGA uses a classification system, with four classes based on the level of risk to the patient and to other members of the public. These are: Class 4 IVD – high public health risk; Class 3 IVD – high personal risk or moderate public health risk; Class 2 IVD – low public health risk or moderate personal risk; and Class 1 IVD – no public health risk or low personal risk. There are guidelines provided in terms of where IVD devices may be placed, but each application to the TGA is currently evaluated on a case-by-case basis. Class 4 IVDs are “those intended to be used to screen for transmissible agents in blood, blood components and tissue for transfusion or transplantation”, and thus currently generally outside the scope of home use POCT devices. Class 3 IVDs are those “used to diagnose serious infectious diseases where there is a risk of propagation in the community, to determine immune status or to monitor concen-
trations of medicines, substances or biological components, where an erroneous result would put the patient in an imminent life-threatening situation or would have major negative impact on outcome. The devices provide the critical or sole determinant for the correct diagnosis. These IVDs may also present high individual risk because of the stress and anxiety resulting from the information and the nature of possible follow-up measures.” These would include, as an example: those used for “ Monitoring concentrations of medicines, substances or biological components when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation. Examples include: cardiac markers, cyclosporin and prothrombin time.” Thus, POCT for International Normalized Ratio (INR) monitoring could feasibly be placed within a Class 3 IVD category. Class 2 IVDs are those that “ detect the presence of, or exposure to infectious agents that are not easily propagated in the Australian population or that cause self-limiting diseases. Class 2 IVDs that present a moderate individual risk include those providing results that are not intended to be used as the sole determinant in a diagnostic situation, or where an erroneous result rarely puts the individual in immediate danger.” Serum cholesterol testing is used by the TGA as an example of a Class 2 IVD.

Although this overview document (13) clearly mentions and incorporates the use of home use IVDs (for example: “ home use IVDs for the detection of pregnancy or ovulation” are placed within the Class 2 IVDs), the specific issue of home use IVDs or POCT devices are likely to be dealt with more extensively in the future. Of interest, the TGA released some draft guidelines for sponsors (i.e., manufacturers or medical supply companies) wishing to release IVD goods for home-use in 2003 (14). The consultation period for those guidelines closed on 1 August 2003. The TGA advised that “ Stakeholders will be advised when the new document is implemented.” It is interesting that as of late 2009 this specific document remains unreleased according to our understanding, although the Website page is currently date stamped as 15 March 2009.

Preanalytical issues

Preanalytical variability, which includes all the phases of the total testing process from test prescription to sample preparation, is traditionally regarded as a critical aspect of testing, where most errors occur (15–18). The preanalytical phase in POCT lacks some critical aspects of traditional laboratory testing, especially sample preparation and handling. In fact, in most test cases the sample is whole blood which does not require centrifugation, separation and storage. As such, the most critical preanalytical issues in POCT are appropriateness of the request, sample collection and test environment (Figure 1).

Considering that POCT is traditionally performed outside the laboratory environment, with little control or audit by laboratory professionals, the appropriateness of the test request is traditionally under the responsibility of the request-

Figure 1 Leading preanalytical, analytical and postanalytical problems in point-of-care testing (POCT).
or volume (e.g., application of an inappropriate volume of sample to the POCT device’s testing surface or reaction chamber). Biological variability (e.g., gender, age, patient/client diet, fasting/non-fasting, circadian rhythm, interference by medications or drugs) is an additional critical issue that should be recognized before performing the test and interpreting results.

The test environment is also regarded as a potential source of preanalytical variability. CLSI specifies some important characteristics of the test environment, that are temperature, humidity, lighting, level and stable work surface. According to CLSI, additional basic components of testing that apply no matter where a test is performed include the person doing the test (tester), testing environment and test materials. Moreover, among the quality system essentials for in vitro testing designed by CLSI, those relevant to POCT include personnel, purchasing and inventory, process control, information management and occurrence management.

**Analytical issues**

The quality of a test performed using either laboratory instrumentation or a POCT device should meet some essential criteria that fulfill the medical purpose for which the test is conducted (Figure 1). Although it is widely recognized that the analytical performance of POCT devices is inferior to tradition laboratory methods, and that laboratory diagnostics performed at sites other than the laboratory has traditionally achieved poorer results, recent advances in technology appear to allow some biology-based goals, which are the appropriate standards to be met (21). The overall analytical variation in laboratory medicine usually embraces two main variables, which are imprecision and bias (Table 1) (22). The imprecision of POCT is traditionally assessed by analysis of results of Internal Quality Control [e.g., replicate results of control sample materials and calculation of the coefficient of variation (CV)]. The comparative bias of POCT is usually investigated by comparison with a reference laboratory method of known bias or, alternatively, by analysis of results obtained in external quality assessment schemes (EQAS) and/or proficiency testing. The available approaches to assess analytical variability have been ordered into a hierarchical framework. This framework has now been acknowledged by experts to be the best current approach to a global strategy for setting quality specifications in laboratory medicine irrespective of the settings in which laboratory medicine is practiced, including POCT (22). Basically, this hierarchy develops through assessment of the effect of analytical performance on specific clinical decision-making, assessment of the effect of analytical performance on general clinical decision-making (including issues, such as the patient outcome, preanalytical, biological and analytical variation), professional recommendations, quality specifications per regulation or by EQAS organizers, and published data on the state of the art (22). Ideally, quality specifications should be derived from analysis of the effect of analytical quality on medical decision-making. However, this is often unattainable since laboratory test results are only one variable influencing the clinical outcome, and they should be weighted against all the others, either biological or environmental. Therefore, in daily practice the acceptable standards of analytical performance required by POCT are traditionally derived from professional recommendations (e.g., the desirable Specifications for Total Error, Imprecision, and Bias, derived from intra- and inter-individual biologic variation) (23), and EQAS organizers, such as those included in the CLIA 1988 legislation which reports acceptable total error for a number of commonly assayed analytes (1). Although the FDA appears to support the use of total error in the clearance of waived tests, FDA statisticians are also discussing the value of evaluating total error against a target, such as an allowable total error, which might be defined by the CLIA criteria for acceptable performance in proficiency testing for POCT. Very recently, some additional standards were developed, including CLSI EP21 (Total Analytical Error), which seems to be widely supported by the FDA for use with “waived” methods. EP21 requires 120 patient specimens to estimate total analytical error for each decision level; given two or three decision levels for most tests. Specimen numbers will often be as high as 240–360, which although feasible for manufacturers, may not be feasible for ordinary laboratory users. The major drawback of quality specifications based upon fixed limits is that, although often based on expert opinion, they tend to be subjective and are affected by the state of the art. As such, quality specification might also be generated comparing performances achieved by groups of laboratories participating in external quality assessment (EQA) and/or PT schemes. This alternative approach has some advantages, including less subjectivity, being reflective of actual practice in the field, and the availability of a larger amount of data. However, this approach might alternatively be biased by the fact that many analytical evaluations of devices are performed in reference laboratories by expert and trained personnel, rather than being performed by staff of healthcare facilities (e.g., pharmacies or wards) who would actually use the instruments in practice. A typical example is that reported in Figure 2, where we compared the effective performances of some POCT devices run by trained laboratory professionals against those achieved by pharmacy-based staff, using identical reference samples. Interestingly, while the analytical performance obtained by the laboratory personnel is generally satisfactory, albeit exceeding the imprecision and bias derived from intra- and inter-individual biologic variation (except for testing of triglycerides), the analytical performance obtained in three different pharmacies were rather heterogeneous, and the imprecision and bias are two to five times higher than those obtained by laboratory technicians (23). These local findings mirror a widespread condition and recognize several causes underlying inappropriate and unsuitable use of POCT devices outside the laboratory. This should prompt clinical professionals and their Scientific Societies to give greater consideration to the importance of developing internal QC and external quality assurance (QA) schemes for POCT, especially when tests are performed in pharmacies. Some examples are already available. The Aus-
Australian Government-funded Quality Assurance for Aboriginal Medical Services Program (QAAMS) provides a framework by which POCT for hemoglobin A1c and urine albumin:creatinine ratio can be performed to facilitate better diabetes management in medical services. The median imprecision for QC testing has continually improved over the years, stabilizing at approximately 3% for both analytes. This indicates that this model is effective in improving the reliability of POCT and can be exported internationally to other clinical settings (24). INSTAND [Gesellschaft zur Förderung der Qualitätssicherung in medizinischen Laboratorien (the society for the promotion of QC in medical laboratories)] has been running EQA surveys for POCT for several years. These have been primarily, but not exclusively, concerned with the measurement of blood glucose and qualitative urinalysis. Results of this trial clearly demonstrate excellent long-term stability of results as tested by repeated distribution of the same materials over a 12-month period, demonstrating that the performance of POCT devices under “controlled” conditions is satisfactory in terms of result-comparability (25). The EQA of POCT of blood glucose has also been assessed in 193 Ontario acute care health institutions since 2001. Results are encouraging and demonstrate that the number of results flagged for bias has decreased since the beginning of the program (26). Most recently, an EQA scheme for POCT has been customised to meet the demands of high street pharmacies in the UK. Over 500 packages are sent weekly to participants, with variable and multiple sample requirements. The EQA programs are designed for ward staff, primary care nurses, occupational health staff and pharmacists, and covers training, EQA and problem solving (27). Data from EQA exercises involving users of several different POCT-INR devices for monitoring oral anticoagulant therapy are also available, demonstrating the feasibility of this approach for therapeutic drug monitoring (28). The Royal College of Pathologists of Australasia (RCPA) Hematology Quality Assurance Program (QAP) also conducts a POCT-INR EQA proficiency program (29), primarily for laboratories but also for general clinical practitioners. There has also been recent interest from the pharmacy profession. Interestingly, although INSTAND runs EQA for several POCT processes as noted above, it has...
decided not to provide an EQA for home-use POCT-INR. This is due primarily to the overwhelming number of users of such instrumentation and the difficulties associated with providing such a service (30). In any case, the discussion of the results from these QC programs should lead laboratory professionals to better address the importance of education, training and retraining programs. This should allow for effective certification of personnel performing POCT in pharmacies, so that quality and safety for patients and customers can be granted. In the year 2002, waived laboratories that were part of the CDC Laboratory Sentinel Monitoring Network project in the states of Arkansas, New York, and Washington were surveyed about their QC and QA practices when performing waived testing. Remarkably, only half of waived laboratories follow manufacturer’s instructions for recommended QC and QA. These results demonstrate that imposing good laboratory practices by regulation alone might be insufficient to ensure quality laboratory results in any location evaluated (31). Between 2002 and 2004, the CMS surveyed 4214 CW sites, showing that although the majority were aware of and followed some practices for ensuring the accuracy and reliability of their testing, lapses in quality were identified at certain sites, some of which could result in patient harm. In particular, the survey found that 12% of the sites did not have the most recent instructions for the waived test systems they were using, and 21% did not routinely check the product insert or instructions for changes in information. According to manufacturer’s instructions, 21% of the CW sites did not perform QC testing as specified, and 18% did not use correct terminology or units of measure for reporting results. Other quality deficiencies identified included failure to adhere to proper expiration dates for the test system, reagents, or control materials (6%), failure to adhere to the storage conditions as described in the product insert (3%), failure to perform follow-up confirmatory tests as specified in the instructions for certain waived tests (6%) and failure to perform function checks or calibration checks to ensure the test system was operating correctly (5%) (32). Additional problems that might arise from inadequate or inappropriate competency/education are (i) omitted, non-protocol, or incorrectly entered calibration, (ii) interference, specimen-related non-target influences, specimen–reagent, (iii) the lack of required QC performance, and (iv) the failure of POCT operators to recognize out-of-range QC values (33). Ideally, a competent analyst in the traditional laboratory setting can often overcome or at least recognize and mitigate these shortcomings, but this might not necessarily occur when the tests are performed outside the laboratory by less expert and trained personnel.

While using waived test systems, CLSI specifically mandates that the characteristics of self-testers should include reading and adherence to manufacturer’s instructions. Also, the characteristics of the test materials should include robustness at temperature and humidity extremes, shelf life, test instructions, packaging and configuration and the specimen collection device. Recently, the American Association for Clinical Chemistry (AACC) has issued some considerations on the appropriate use of POCT devices. Along with the FDA, the AACC strongly encourages that manufacturers demonstrate in the CLIA waiver application that sources of error are controlled or mitigated by fail-safe or failure alert mechanisms (fail-safe mechanisms are designed with a lock-out function that will ensure that a test system does not provide results when tests are inappropriately conducted or where the test result is based on faulty test systems). The AACC also recommends that all devices approved as waived make available to users a scientifically detailed description of the analytical method, which should not be necessarily included in the package insert, but should be available on the company’s website by a specific reference included in the package insert. The level of detail should be sufficient that a scientifically knowledgeable user can evaluate the performance of the device. While the FDA already encourages manufacturers to develop training and education programs to promote good laboratory practice among end operators, it further recommends that the label instructions include an explanation of the differences between what “must” and what “should” be done using waived test systems (e.g., CLIA having a CW and following the test system instructions) from a regulatory standpoint, since those words, particularly “should”, are used repeatedly through the document and have different meanings and consequences. Further issues to be considered according to the CAP include promulgating goals, making good calibration materials widely available, and developing QC, quality assessment, and quality management, all of which are required to ensure that the desirable performance standards are obtained in all locations in the future (21). It is also important to note that the use of whole blood samples for direct analysis and the pertinent technologies might produce different results from those provided by traditional laboratory testing due to a variety of factors including matrix effects, differences in the nature and proportions of chemical reactants and ligands, rates of dissolution and diffusion, metabolite and drug interferences (12).

Postanalytical issues

POCT has the inherent potential to provide faster test results, but whether this translates into a tangible improved patient care is still an unresolved issue (33). Some of the frequent postanalytical problems encountered with POCT are similar to those seen in traditional laboratory testing, but some are instead peculiar. Basically, these can be clustered within four categories, including report formatting (e.g., absent or inappropriate errors in units, reference intervals, machine output, human transmission/transcription), critical value reporting (e.g., critical results unrecognized, not brought to decision-maker’s attention, not documented for retrieval), other result reporting (report communication failed/delayed, lost to retrieval), and report recording/retrieval (e.g., report verification, preservation, storage, and retrieval) (Figure 1) (33).

Carraro et al. recently performed a study to investigate the type, frequency and clinical risks associated with POCT using portable glucose meters in the hospital setting by eval-
leting the postanalytical phase when data are manually transcribed into the patient’s record. By checking all registrations performed by nurses of two selected wards of the hospital during a period of 30 consecutive days (1966 blood glucose determinations), the authors observed that data obtained were often not reported in the patients’ files (12.1% of results were missed), the time of blood sampling was recorded in an imprecise manner (7.2% of cases) and the glucose concentration was incorrectly reported (3.2% of results). Although in the postanalytical phase the frequency of incomplete or incorrect data was high, no adverse events could be related to this type of error (34). An additional study by Tighe [reported during the European Conference on Quality in the Spotlight in Medical Laboratories (Antwerp, Belgium)] utilized an EQA program for capillary blood glucose and “dipstick” urinalysis to investigate postanalytical errors of result interpretation by various grades of nurses performing POCT. When the results simulated either a hypoglycaemic or hyperglycaemic patient, 84% and 97% of nurses interpreted the results correctly, respectively. However, in the simulation of a case where the capillary blood glucose was falsely increased due to puncture site contamination, only 5.4% of nurses interpreted the POCT results correctly. As the seniority of the nurse made little or no difference to the interpretation given, this study clearly demonstrates the need for improved training (35). Another crucial issue is the lack of knowledge that some pharmacists might have concerning the important features of screening tests, such as false-positive and false-negative rates (36).

Selection of the appropriate units of measure and reference ranges is another crucial issue. Typical reference ranges can be identified from clinical guidelines or from manufacturer’s instructions. However, it should always be considered that, given the different analytical techniques, some POCT devices might require reference ranges or threshold values different from those reported in clinical guidelines or recommendations. The CLSI specifically mandates that the self-tester should evaluate results and take appropriate action. This is in agreement with the basic concept that all healthcare providers should develop clear strategies around unique expertise and tailored facilities in those areas where they can become distinctive, in order to prevent “ commoditization” of testing (37). Therefore, laboratory professionals should actively participate in the development and implementation of decentralized testing in any possible environment (including pharmacies), since they are in a prominent position to provide assistance for creation, distribution, and application of knowledge related to laboratory aspects of patient care (38). Therefore, once the patient has been educated on the interpretation of results, rational follow-up should also be assured. If the result is within normal ranges, follow-up may be a recommendation regarding the next time that the patient should be screened. Conversely, when the result is abnormal, the follow-up might imply referral to another healthcare professional, such as a general practitioner or a specialist.

Connectivity means connection to a laboratory information system, the hospital information system, and the electronic patient record. It is undeniable that POCT connectivity, as for traditional laboratory testing, would be effective in reducing user (transcription) error, increase program compliance, decrease POCT coordinator and nursing costs, facilitate recognition and communication of critical values, make results more widely and more rapidly available, often in a more easily and intelligible forms, and store data for longitudinal comparison. Standardization in this area was originally addressed in 1998 by the POC Testing Division of the AACC and members of the IVD device industry. By the year 2000, this had evolved into the Connectivity Industry Consortium that included representation by various standards development organizations including CLSI, ANSI Health Level 7, and IEEE (39).

Conclusions

POCT is a rapidly growing field in clinical diagnostics. It is reasonably considered to be one of the main driving forces for the future of IVDs due to some technical features that include ease of performance, minimal technical expertise required, rapid measurement (allowing earlier diagnosis and therapeutic actions), use of whole blood specimens or urine with no pretreatment, low maintenance (or disposable), and improved convenience for the patient (e.g., time savings, less painful sampling). In recent times, POCT devices have become available to several facilities, some located outside the traditional hospital environment (physician’s office, pharmacy, supermarket), thereby introducing new challenges and new sources of potential errors (33). Therefore, as we move forward in this dynamic and fast growing area, it is important to remember that no device is “foolproof”, that errors can always occur, and that appropriate resources should be allocated to quality management for influencing patient care in a positive way (40). Understandably, the traditional diagnostic errors might be enormously magnified with POCT, not only because of increased numbers of analytes, but also the availability of so many waived test methods employed outside the safety net of the traditional centralized laboratory setting (41).

It is widely acknowledged that the process of POCT reduces errors and the risk of error to only a few steps of the total testing process. Basically, POCT technology might be helpful in the preanalytical phase for reducing patient and specimen misidentification, sample handling and storage, and in the postanalytical phase for limiting routing and excessive turn-around time. Other typical laboratory errors might alternatively be amplified by POCT, such as misinterpretation of biological variables, collection of appropriate samples, environmental conditions (e.g., altitude, humidity, temperature), method calibration, patient-related “native interferences”, specimen-related “non-target interferences”, specimen-reagent combination-related “matrix effects”, result generation (e.g., results outside validated ranges), quality assessment (by EQA schemes, or proficiency testing), and results management (33). The presence of some further “amplifiers”, such as incoherent and non-standardized regulations and failure of clinician/caregivers to respond appro-
priately to POCT results might make the situation even worse. According to these data and likewise other areas of testing, simply focusing on reduction of analytical uncertainty without considering the whole POCT process has limited benefit on the clinical value of test results, since the contribution of the extra-analytical variability is frequently the major factor contributing to uncertainty in POCT. The most effective strategy to achieve efficiency, efficacy and safety of POCT would thus require a multifaceted approach, which encompasses cost analysis, continuing education of operators, appropriate usage and maintenance of the device, verification and communication of test results.

First and foremost, comprehensive analysis of the cost-to-benefit ratio should be planned before implementation of new waived tests in pharmacies or other extra-hospital settings for both economical and clinical reasons. Currently, there is a tendency toward unrestrained and often frenzied implementation of POCT by health administrators, perhaps persuaded by unrealistic and exaggerated benefits of simple, waived tests. These benefits include the potential for diagnosing and treating the patient earlier, obtaining an easier count of workload, reducing overall health care costs or achieving a more favorable recoup of expenditures. However, a cost analysis of implementing a POCT should encompasses the cost of the test per patient compared with standard laboratory procedures, as well as the economic impact on patient care and total healthcare expenditures. Because there are no established standards for evaluating costs of this testing, it is ultimately challenging to establish its definitive economic impact. Compared with tests performed in traditional core laboratories, the cost of POCT has now been reported to be much greater (up to 10-fold higher) due to the lower volume of testing and the added cost of the unit-dose packaging (42–45). However, the increased cost may be offset by improvements in the management of patient care, improvements in patient outcomes, and decreased utilization of the healthcare system (5). In this respect, the clinician/caregiver test utilization paradigm should be substantially modified to rationalize implementation and take full advantage of resource utilization and POCT results available on site in real time, instead of concentrating solely on the cost per test. With regards to pharmacies, it should be primarily assessed that the service fits the needs of the current environment before a POCT service is instituted. This involves a typical SWOT analysis, which helps identify the Strengths, Weaknesses, Opportunities, and Threats surrounding the current practice. The main aspects to be investigated are the presence of additional local resources that may already provide some POCT services, the demographic characteristics of the patients, and the prevalence of disease for which the tests are being implemented. This would help establish not only whether a certain test might be indicated in a given geographical area, but also if the device would meet the identified population’s needs, as well as the needs of the pharmacy. Potential internal and external barriers should also be identified, as well as the interest and potential for involvement in the service by patients, health care providers in the community, and pharmacy staff. The collaborative opportu-

nities with hospital wards and local physician offices should be addressed to establish the real effectiveness of testing. Finally, the overall cost of the device and testing procedure (utilities, occupancy, inventory costs, and liability insurance) should be carefully examined, since different options might be available (e.g., POCT might be purchased, leased, or a pre-owned machine can also be bought to decrease the initial costs of starting a program).

Manufacturers should be proactive in incorporating consensus security, validation, performance, and emergency systems, error reduction options (e.g., internal QCs, software-based safeguards) into instruments. Thus, all users might have the necessary instruments to improve the safety of POCT and to test objectively the manufacturers’ claims of accurate and precise performance. Subsequently, educational approaches developed by either laboratory or non-laboratory personnel is essential. The former will provide non-laboratory personnel with meaningful information on the preanalytical and analytical issues (e.g., patient preparation, sample collection and handling, biases between POCT devices and standard laboratory testing methods, analytical quality, interferences). Non-laboratory personnel, however, might propose and utilize teaching vocabulary and evaluation formats that are effectively comprehensible to the staff performing waived testing.

According to Kost, expert specifications for prevention of POCT errors include: (i) adoption of operator certification, validation of POCT programs, adherence to regulatory guidelines, (ii) implementation of security, maintenance, validation, performance, and emergency systems on existing and new devices, (iii) use of flexible, user-defined error-prevention system options on instruments as a prerequisite to federal licensing of new diagnostic tests and devices, (iv) integration of connectivity standards for bidirectional information exchange, (v) preservation of fast therapeutic turn around time of POCT test results, (vi) control of invalid use (e.g., by using of a series of integral controls and calibrators contained in validated, closed reagent packs and multiple sophisticated computer-initiated and -driven algorithms, so that the system would not be allowed to release patient’s data when pre-established quality criteria are not fulfilled), (vii) operator competence, quality compliance, and (viii) other performance improvement (e.g., absolute adherence to established testing protocols designed to minimize the likelihood of error, selection of test systems that identify, intercept and/or correct any process malfunctions, standardization and/or harmonization of results with traditional laboratory assays and among different devices, and adherence to regulatory guidelines) (46). To fulfill these standards, all procedures related to POCT usage should be clearly written, including (i) purpose of the tests (screening, diagnosis, monitoring), (ii) principle of operation, (iii) specimen collection, identification and handling, (iv) preparation of reagents and other materials, (v) QC procedures, (vi) stepwise instructions, (vii) reporting and documentation of results, (viii) special alerts to out-of-control and “critical result” values, (ix) limitations of the procedure, (x) remedial action when out-of-control, (xi), reference interval, (xii) reagent, test unit(s), and material
storage, (xiii) actions if the test system is inoperable, (xiv) criteria for referral of specimens to an accredited laboratory for confirmation, (xv) criteria for data recording, and (xvi) procedures for interpreting results and counseling. Regular assessment of instrumentation maintenance/functionality is necessary. Preanalytical, biological variability and analytical bias should also be clearly acknowledged and taken into account by users for correct interpretation of a test result. Proficiency testing or an external program for evaluating the accuracy of the POCT system (equipment, reagents, and operators) is also advisable, if not mandatory to systematically verify accuracy and precision of data (according to CLIA 1988, a baseline of ≥80% success for any specific analyte in proficiency testing or EQA should be set). Preferably, this should be performed by the same mix of test operators (e.g., physicians, pharmacists, or office staff) who actually perform routine testing. Otherwise, we might face a paradoxical situation, where traditional laboratories with well-trained staff are subjected to strict regulations (certification, accreditation), while wide deregulation might allow decentralized testing by less trained individuals without any quality assessment.

Given the outstanding advancements in medicine, technology and computer science, along with the ever-growing requests for in vitro testing and the profound reorganization of laboratory networks worldwide (consolidation, integration, outsourcing), there is no certainty on the future of laboratory diagnostics. However, it is predictable that the current monopoly situation of hospital and private laboratories can be seriously challenged by on-site, mobile and even “virtual” laboratory testing services, which will offer tests at more competitive prices and in a manner that is more comfortable for the patient. Moreover, recent advances in the new fields of “omics” will soon make available a vast array of novel biomarkers. Measurement of these biomarkers on a single and rapid test platform (for decreasing the turn around time, allowing early diagnosis and immediate start of treatment) might make healthcare delivery more efficient compared with use of conventional laboratory testing. Therefore, POCT patient care service in pharmacy can be regarded as a valuable option for the present and the future. This might be beneficial for all parties (patients, healthcare system and pharmacy), providing that a core set of Competency-Quality-Consultancy prerequisites are fulfilled (38). Moreover, some economical, clinical and regulatory issues should also be addressed before this opportunity can turn into a real advantage for the patients and the entire healthcare system. Finally, the most appropriate allocation of POCT within the diagnostic pathway, as well as its adjuvant role in screening, diagnosis and monitoring of diseases should be clearly established in order to prevent widespread and deregulated implementation.

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