Total quality management in the \textit{in-vitro} diagnostic

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SUMMARY

Clinical laboratory activity relies on quality assurance for all steps from the sample collection to results reporting. In the preanalytical phase, sample handling presents many key points, such as collection, identification, transportation, reception, sorting, centrifugation or aliquoting. Concerning the workcell, metrology, maintenance, quality controls, and proper written operating procedures associated with records should achieve the goals for a total quality management of the \textit{in-vitro} diagnostic.

KEY-WORDS : quality assurance - \textit{in-vitro} diagnostic - preanalytical - metrology.

Introduction

Clinical laboratory activity used to be defined as a qualitative or quantitative determination of an analyte or a cell in a biological sample. Analytical systems, data processing, quality control, and a good know-how were necessary to perform sample analysis. Nowadays, all the steps from sample collection to the reporting of test results to the practitioner and the patient are included in quality assurance. These steps can be presented as a "quality loop", including some key issues:

- The sample must be collected in the right container, according to any physiological variation or drug interference.
- Samples must be transported without damage to the laboratory, avoiding mechanical, thermal or delay problems.
- By accepting one sample, the clinical laboratory assumes that this sample is identical to the one collected. The laboratory produces validated results, and reports them within a minimal delay with some eventual service assistance in the interpretation of the results.

This is particularly relevant as many laboratories are merging in order to face cost containment, thus amplifying sample handling, automation, and information processing. This enlargement of the responsibility of the laboratory induces to reorganize the laboratory process, as it is the case in many other activities.

Sample handling

Subject preparation, sample collection and handling have been extensively discussed in various guidelines and in the literature [5]. We would like to study the process of sample handling and present some critical points and give some laboratory engineering answers.

From sample collection to its storage or disposal, the sample handling process follows successive steps:
SAMPLE COLLECTION

Many guidelines discuss the choice between plasma and serum; many other aspects like plastic or glass tubes, tubes with gel or activators, should be evaluated by each laboratory before giving operational procedures for sample collection. Special care should be given to identification to avoid any mismatch between samples. Many systems are available, from the simple barcode to electronic labels which can store many data relative to collection and other preanalytical steps [1].

SAMPLE TRANSPORTATION DEVICES

The so-called “room temperature” should be avoided. For whole blood immunoassays, it is necessary to establish good thermal control with temperature verification, to control at + 4°C or + 20°C within acceptable limits. For serum or plasma, if transportation in the frozen state is necessary, it is important to freeze the samples for at least two hours before transportation; the transportation device should not be used as a freezing device. We recommend, as it is done for transportation of human blood bank products, to use adapted vehicles with three compartments (+ 4°C, + 20°C, - 20°C). These compartments can easily be achieved in a air-conditioned car (+ 20°C) equipped with a low-voltage refrigerator (+ 4°C), and eventually dry ice (- 20°C). Verification of temperature control is assured by sensors which record the temperature, and are placed inside the containers.

RECEPTION AND SORTING

The delay between sample collection and result transmission is an important issue. The arrival time in the laboratory should be recorded; it is different from the data input on the laboratory information system. If good thermal control was obtained during the transportation, it should not be lost before the analytical step; the reception area is often a critical step for sample preservation. With respect to carryover, sample holders may be the cause of carryover if they are not cleaned after each use to bring samples from the reception area to the laboratory; the ideal answer is to use disposable test tube holders.

CENTRIFUGATION

For safety reasons, we recommend to centrifuge in an isolated area, using centrifugation baskets equipped with a closed cover to avoid aerosols in case of tube breakage [4]. In this case, the centrifugation baskets are opened in a safety cabinet using special gloves protecting the operator from any sharps. For the same safety reasons, we do not recommend robotic handling if the robotic system is unable to detect a tube breakage.

SAMPLE ALIQUOTTING

Since it is often necessary to store an aliquot of the sample, and since manual aliquotting is time consuming and biohazardous, automation of aliquotting is a priority for many laboratories. However, the following items should be covered:

- Cap removal must be safe and carryover between adjacent tubes in the tube holder must be avoided.
- Before aliquotting, the barcode labels of primary and secondary tubes must be checked automatically to avoid any mistake due to a wrong position of the tube.
- Disposable pipette tips are required to avoid sample-to-sample carryover during the delivery.
- Recapping with a new clean stopper is recommended to avoid any mismatch.
- Clean or disposable tube holders are required.
- After sample aliquotting, there are different alternatives:
  - Storage in a sample bank: the temperature and duration of storage should be validated for each analyte if it is not described in the literature. Then, a written operating procedure should describe how to place a tube in the bank, how to find a tube, and the periodicity of discarding tubes.
  - Submission to another laboratory: depending on the analytes, the temperature of the tubes should be maintained at + 4°C or -20°C, with a record of temperature variations during the transportation. Inside the container, but in a separate packaging, a transmission sheet includes the following information: sample data, time of sample collection, time of sample preparation (e.g., centrifugation), temperature and duration of sample storage before transmission. Upon arrival, the receptionist verifies the quality of the samples.
  - Transmission to the workcell by an automatic conveyor or manually: if storage at + 4°C or -20°C is required, it is important to preserve the sample at this step and to control the internal transportation time.

The workcell

METROLOGY OF THE WORKCELL

We would like to emphasize here two aspects of the Metrology which are especially relevant to immunoassays:

1) The environment of the workcell:

From various industries, we have learnt that good reliability of a manufacturing process greatly depends on perfect control and traceability of environmental factors. The more we are able to reach a low detection limit in analyte determination, the more environmental factors will interfere with the results.

The room temperature must be compatible with the limits established by the manufacturer of the analytical system (specifications). It should be checked and recorded manually or automatically.

In the same manner, the temperature of cooling or warming devices (refrigerators, freezers, waterbaths, etc.), must be controlled in order to verify that reagents and samples are stored or incubated at the right temperature, according to manufacturer’s specifications, and to immediately detect a breakdown.

2) The control and calibration of weighing balances must be performed if reagents are prepared in the laboratory.

3) The volumetric control of pipettes:
When pipetting steps are performed by the operator, pipettes should be periodically checked by gravimetric or optical methods. In immunoassays, metering and delivering small volumes below 20 microliters is often required; thus, we recommend accuracy and precision calibration using an optical instrument. When it is possible to modify the volume delivered by a pipette, we control two different volumes.

4) The quality of the water:

Frequently, so-called technical problems are due to the poor quality of the water (pH too acid or alkaline, microbiologic growth), or to a too pure water (no sample detection, etc.).

When an automated system requires an external input of purified water, it is important to know from the specifications the exact quality of the water which is necessary. The corresponding water treatment system is installed beside the instrument with control devices whose results will be checked daily.

MANAGEMENT OF THE WORKCELL

We can distinguish different steps which are usually met in the management of an analytical workcell. A work sequence is defined with decision steps; in cases with multiple decision steps as manual methods, it may be useful to design a checklist which summarizes all the points which have to be checked by the operator. Corresponding operating procedures are included which explain the technical tasks, and try to anticipate the problems and provide solutions to these problems. The records certify the daily work was performed in accordance with the quality system. It is necessary to detail some steps:

REAGENT PROCESSING

Nowadays, to allow infrequent or reduced calibration, most of the reagents are available in various stabilized forms like liquids, powders or lyophilized particles, suspensions of magnetic or latex particles. In immunoassays for instance, the main reagents are conjugate (labelled antibodies in solutions), solid phase (coated antibodies), diluents, calibration solutions, signal reagents, and buffers.

Just before use, some of these forms must be reconstituted or resuspended manually or automatically. Sometimes, the operator has to manage two different lots of reagents for the assay of the same analyte. If the number of reagents on board is limited, the operator will have to load and unload the reagents back and forth between the refrigerator and the analytical system. The role of the operator is crucial with a strict application of the operating procedures and maintaining the records of the reagents stocks.

Besides the throughput, a very important requirement is the continuous free access to the analytical system to load the reagents. During the loading, the automatic identification of the reagents by the analytical system will inform the operator if the reagent is expired, if the reagent lot is known and if it is calibrated.

SAMPLE PROCESSING

Before loading the samples, the optical quality of the sample must be checked (e.g., hemolysis, turbidity, hyperbilirubinemia), but also the medical and biological history of the patient should be reviewed in order to anticipate an analytical overrange and eliminate a risk of carryover by diluting the sample.

Some analytical systems have the capability to perform reflex testing when this function is activated by the operator: we would like to emphasize that, for automated systems with continuous sample loading and unloading, this feature is functional only if the system has the capability to pick a sample or a rack from the unloading area and move it to the analytical area.

TRACEABILITY OF CALIBRATION, QUALITY CONTROLS, AND SAMPLE RESULTS

Since some stabilized reagents use the same stored calibration curve for several weeks and that random access automated systems only use a limited number of quality controls, it is crucial that, at any time, on user request, any patient result may be associated with the corresponding calibration curve and quality control in order to assess the quality of the result. Even in case of rapid tests or systems with embedded quality control, it is important to perform independent or "external" controls using known samples tested in normal analytical conditions.

TECHNICAL AND MEDICAL VALIDATION

The criteria of technical validation are based on the scientific and clinical expertise of the laboratory staff. They must be the result of a collective consensus and clearly explained in an operating procedure approved by the team. An important evolution is that test results are monitored in the same way as drug monitoring. The clinical validation consists in considering the results among the complete file of the laboratory results (Hematology, Bacteriology, etc.).

MAINTENANCE

The classical definition of maintenance is to maintain or restore an instrument in a specified state where it is able to deliver a given performance [2].

This definition implies several requirements:

— Before purchasing the immunoassay system, the laboratory supervisors defined the required level of performance based on the medical needs.

— At the installation of the system in the laboratory, the performance was checked and various indicators including quality controls were established to assess the performance throughout the life of the instrument: examples of indicators other than quality controls are precision tests, carryover tests, control of the optical device, and control of the temperature of incubation.

— Periodically, but also after any instrument breakdown, the user must check the performance by using the indicators.
- For any patient result, the user must be able to prove that the instrument has been perfectly maintained; the modern computer interfaces of the immunoassay automated systems greatly help in maintenance traceability.

WASTE MANAGEMENT

An important task of the operator of an analytical workcell is to sort the different kinds of produced waste: liquid waste, solid waste (disposable tips, cuvets, etc).

The goal is to decrease waste handling, identify and contain biohazard [3].

Besides biohazardous materials, some papers may contain confidential information concerning the patients. They must be discarded to ensure confidentiality.

The process of waste management from the production at the workcell to the final destruction by a contracting specialized company must be known and traceable by records about waste transportation and destruction. All the staff involved in this process must be informed about biohazard and wear protective equipment (gloves, etc.). If there are several laboratories in the same site, even at different floors of a building or in separate buildings, the biohazard warnings on the containers must be the same.

ERGONOMY OF THE WORKCELL

The ergonomy of the workcell starts from the generic diagram about the interface between the operator and the machine, with the cycle:

— Command from the user through a keyboard or a touchscreen. The user loads or unloads the machine, manually or automatically.

— Execution of the test process by the machine by an action or by a modification in the configuration of the software.

— Display of the result of the execution of the command by a display or a printer.

— Interpretation of the results or of the information by the operator, completed if necessary by consulting some procedures or the user manual, eventual decision making and start up of a new command, and so on...

Many improvements have been made to improve the ergonomy of immunoassay automated systems:

— User interface: Windows NT interfaces, soft colors, attractive and simple icons helping direct access to the required information or function, easy to interpret quality control diagrams and calibration curves easy to interpret, user manuals integrated in the software, etc.

— Safe loading and unloading, with continuous access to the system.

— Decreased noise and improved user safety by limiting access to the robotic area while the instrument is performing assays.

Conclusion

Nowadays, analytical skills and clinical knowledge are not sufficient to establish the quality of the clinical laboratory. Laboratory professionals have to prove that all the steps from sample collection to issuing results are under control, using a total quality management system.

References


