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## Quality Assurance in the Preanalytical Phase

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### 1. Introduction

The preanalytical phase includes a set of processes that are difficult to define because they take place in different places and at different times. Classically, the preanalytical phase included all processes from the time a laboratory request is made by a physician until the sample is ready for testing. While this definition is very informative, errors that occur at this stage often become apparent later in the analytical and post-analytical phases. For example, interference effects for a given sample can be detected during the laboratory analysis or during clinical interpretation. Therefore, current recommendations call for the laboratory error to be defined as the defect occurring at any point in the cycle, from request to interpretation of results by a clinician.

The main processes that should be taken into account in the study of the preanalytical phase are: test selection; patient preparation; collection, transport, handling and preservation of the sample; and interferences. The study of the characteristics of individual patients and the biological variation for each laboratory test belong to this phase, too.

It has been documented that laboratory errors have significantly decreased in the last four decades, especially those that occur during the analytical phase; furthermore the scientific evidence reveals that most laboratory errors occur in the preanalytical phase. The large majority of laboratory errors occur in poorly standardized or manual processes. Preanalytical mistakes account for up to 70 % of total laboratory errors. The magnitude of the effect of these errors on patient care is not negligible, since information provided by clinical laboratories affects up to 60-70% of clinical decisions. The current focus of health care institutions on improving patient safety has given rise to a renewed interest in the preanalytical phase. Improvement of preanalytical processes currently constitutes a challenge to be faced by clinical laboratories.

While quality control systems designed to ensure the quality of the analytical phase are highly developed and in use at most clinical laboratories, this is not the case for the preanalytical phase. One reason may be that laboratory professionals have always considered the analytical phase (but not the preanalytical phase) to be the most important process in their profession. Outsourcing of the sampling process could be another cause. Both of these factors have resulted in a decline in quality, as evidenced by an increase in pre-analytical errors, and in turn, these errors have required that quality control systems be

established for the process, such as registration and notification of the errors detected at the collection sites and sampling.

One factor that may also explain the increasing interest in quality control of the preanalytical phase is the ISO 9001: 2008 or ISO 15189: 2007 certification. These standards directly affect the need to define all laboratory processes, including preanalytical ones, and in establishing quality indicators for each process.

Study of the preanalytical phase is of emerging interest as evidenced by an increase in the number of publications in recent years. This chapter describes the most important variables involved in each of the processes of this phase, as well as those quality control mechanisms that should be established in order to minimize laboratory errors and improve patient safety.

## 2. Analytical test request

The most important variables requiring quality control during the test requisition process are identification of the patient and physician/clinical unit, and the tests requested. The ISO 15189 standard specifies the information that must be provided on the request form, regardless of whether the test requisition is made on paper or electronically:

- a. unique identification of the patient;
- b. name or other unique identifier of physician or other legally-authorized person;
- c. type of primary sample;
- d. tests requested;
- e. relevant clinical information about the patient necessary for interpretation purposes; at a minimum, this should include gender and date of birth;
- f. date and time of primary sample collection;

*Failure to identify the patient, or incorrect identification of the patient* could have serious consequences in the clinical decision-making process and may affect patient safety, and for this reason it should be considered a key indicator in the process.

A study published in 1993 found that up to 6.5% of preanalytical errors were due to incorrect patient identification prior to specimen collection (Renner et al., 1993). In 2002, the same authors published the results of a second study showing a large improvement—attributed mainly to participation in external quality assessment programs—in this indicator (Howanitz et al., 2002).

The most important identification errors that occur during the laboratory test request process may be due to patient identification errors (patient misidentification, errors in interpreting demographic data, or in the coincidence of having two patients in the waiting room with the same name and surname) and errors made by the physician when filling out the request form (requesting a test for a patient other than the one currently in the doctor's office). Patient identification errors can also occur during scheduling for sample extraction (Figure 1).

*Failure to identify or misidentification of the physician or requesting unit* may make it impossible to return the test results or the test report may be sent to the wrong physician, leading to complaints, and necessitating that a copy of the original report be sent. The implementation of computerized medical records linked to the Laboratory Information Management System (LIMS) minimizes these types of errors because the data are sent electronically to the LIMS.

*Ordering inappropriate tests* is another preanalytical variable that negatively impacts patient safety. Estimates of inappropriate test requisition vary considerably and range from 4.5% to 95% (Van Walraven & Naylor, 1998). Some factors that contribute to inappropriate laboratory utilization may include:

- Unnecessary repeat testing: it has been estimated that up to 30% of laboratory tests ordered each month are repeat tests (Van Walraven & Raymond, 2003)
- Overconfidence in laboratory test results
- Requests for multiple tests that are basically equivalent in their disease-detection capacity
- Quick and easy access to laboratory directory as a result of the use of new technologies.
- The addition of new tests without studies proving their clinical utility.
- Use of obsolete tests that have been replaced by tests with a greater diagnostic efficacy.
- Industry pressure.
- Little training of clinicians in understanding the diagnostic utility of laboratory tests
- Increase in patient knowledge of health issues thanks to the use of new information technologies. A survey carried out in Europe shows an important increase of internet users had used the internet at some point to look for information about health-related issues (36.3% in 2002 to 50.6% in 2005) (SIBIS Project:2002).

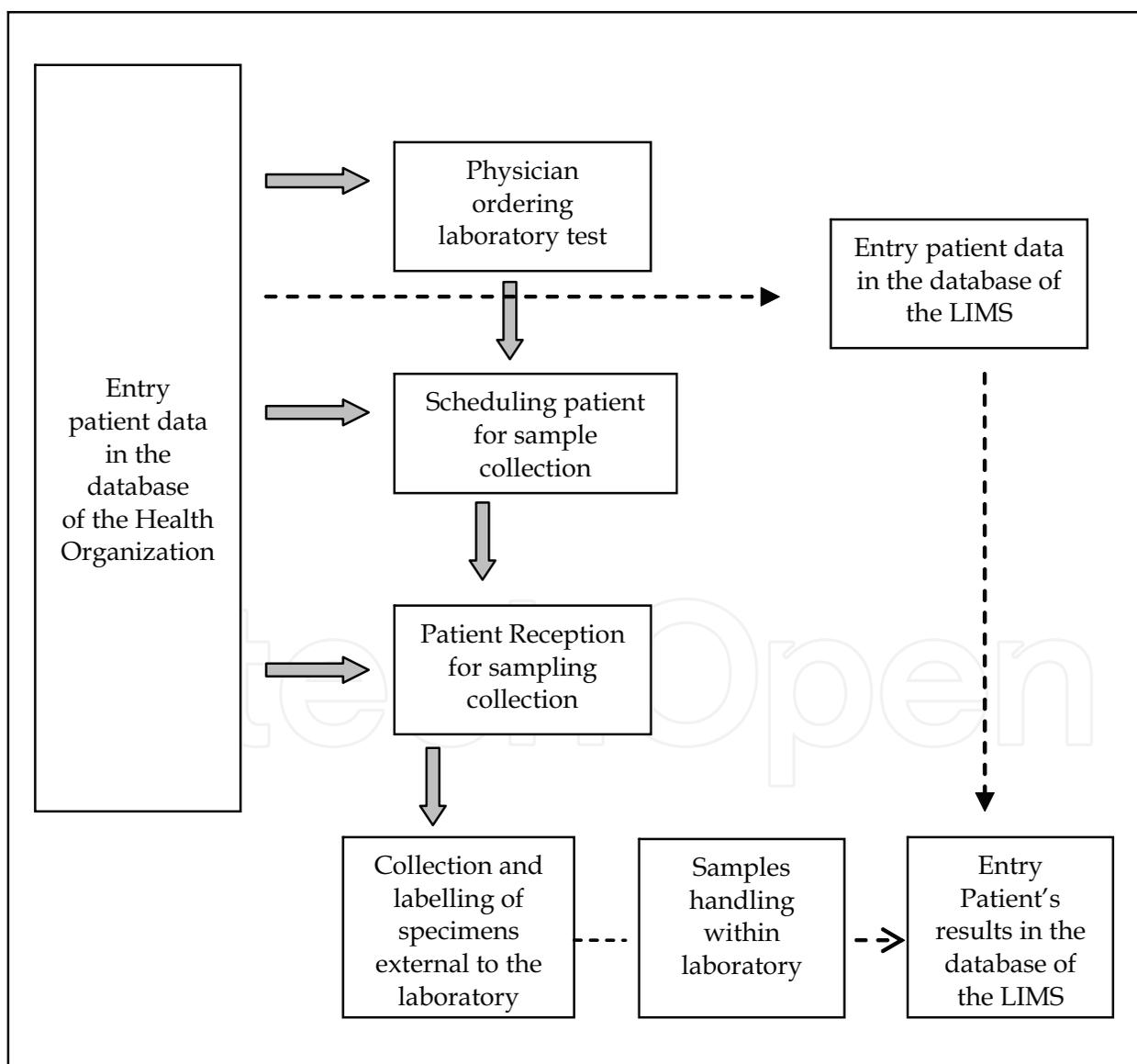


Fig. 1. Points of misidentifications patient data in laboratory diagnostic

Indiscriminate test requisition increases diagnostic uncertainty for the physician, discomfort for the patient, and laboratory expenses. Laboratory utilization can be improved through a variety of strategies:

- Development of test request protocols specific to each pathology, using recommendations from evidence-based clinical practice guidelines and based on mutual consensus between laboratories and clinicians. Despite efforts made in recent years to implement the use of these guidelines, some studies have found clinician compliance to be scant (Salvagno et al., 2007)
- Establishing the use of diagnostic algorithms (reflex testing) in laboratories depending on the disease or the patient's health status.
- The use of expert systems that serve as a connection between the clinician and the laboratory and that act as an aid in appropriate test selection and interpretation. The implementation of computerized medical records connected to the LIMS is quite useful in helping the physician to select the most relevant analytical tests. For example, attaching clinical practice guidelines to medical records improves the relevance of the requested tests.
- Information provided by laboratory specialists to clinicians about diagnostic utility of the laboratory tests, removing obsolete tests from the laboratory's menu of available tests and also those tests that have the same diagnostic value.

Another factor to consider in the test request process is the supplementary information provided by the clinician on the test request form sent to the laboratory: that is, the *individual characteristics of the patient*, such as age, gender, race, physiological conditions such as pregnancy or menopause, dietary and toxic habits, physical exercise, medications, and suspected diagnosis. These data are necessary to assign the correct reference values and avoid unnecessary test repetition in case of incongruent results that cannot be evaluated due to lack of information.

Laboratory professionals, for their part, should provide clinicians with data on the magnitude of biological variations, which may be quite useful in both preanalytical (test selection) and postanalytical (interpretation of test results) processes. It is important that clinicians understand the concept of biological variation, which includes intra-individual biological variation (fluctuation of results around a homeostatic set point of an individual) and inter-individual biological variation (variation between different individuals around a homeostatic set point). An understanding of biological variation plays an important role in selecting the most appropriate test in cases where 2 or more tests with the same diagnostic value are available, since it is always advisable to choose the test with the smallest degree of biological variation. This knowledge is also quite useful in interpreting test results, especially for follow-up; if the range of intra-individual biological variation is very small (tight range of homeostatic equilibrium), such as it happens with calcium, a minimal difference between two consecutive results might be significant; on the other hand, if the magnitude of intra-individual biological variation is large, as it occurs with amylase, the difference between two consecutive results must be much greater to reach the same level of significance.

Most laboratory test results have a high individuality, or to put it another way, a very small intra-individual biological variation compared to the inter-individual biological variation. In these cases, the use of reference intervals is of little use and therefore results should be compared with previous results in the same patient because this allows for significant changes to be detected even when the result falls within the reference interval for the population.

The advent of computerized test requesting has reduced some of the errors that occurred when requests were paper-based, as noted in a study that evaluated the evolution of quality indicators of key laboratory processes over a 5-year period; in that study, the error rate for test requests fell from 4.1% to 3.3% (Alsina et al., 2007; Llopis et al., 2010). However, due to the ease of access (i.e. electronic) to the laboratories' catalogue of services, the number of tests ordered has increased substantially, and many of these tests are not justified by the suspected diagnosis, a fact that will oblige laboratories to establish new controls over this process.

The role of the laboratory in the test requisition process should be more interactive: not only should the laboratory be involved in defining the catalogue of available tests, designing the request form, and implementing protocols based on clinical practice guidelines, but also in negotiating with clinicians to reach a consensus on these variables. Reliable indicators for test requisition quality will need to be established in order to monitor this process.

### 3. Patient preparation prior to sample collection

The test requisition process involves many variables, which is why it is quite complex; this complexity increases further when another variable is added, such as patient preparation to the process, as the number of variables multiplies. The difficulty resides in determining how to generate and transmit this information to the patient, and especially how to assure compliance given that the laboratory is only indirectly involved in this process. The ISO 15189 standard obliges the laboratory to have a preanalytical procedure manual that provides clear directions on the instructions given to patients prior to specimen collection. Some of the variables that patients must monitor are, among others, fasting, diet, physical exercise, stress, wakefulness, and medication. With the computerized test requisition, instructions given to the patient prior to sample collection can be individualized so that the information provided is specific to the tests ordered. Due to the lack of reliable indicators, currently clinical laboratories cannot guarantee the quality of this process; the only control that they have over the entire process is the patient's word regarding compliance. In addition, in the case of laboratories with decentralized collection centers, the laboratory does not know if all off-site specimen collection centers routinely ask patients to confirm protocol compliance. The laboratory should standardize this information in the form of a checklist and train staff to use it properly; an electronic incident reporting system should also be established. **Figure 2** shows an example of preparation instructions given to patients prior to sample extraction for prolactin measurement.

1. **IMPORTANT:** In order for this test to be carried out, you need to be awake 2 hours before the blood is taken, but you must not do any exercise or exert yourself during this time
2. The day before the test you should avoid food which is rich in proteins
3. The day before the test you should avoid any breast stimulation
4. You must not eat or drink anything during the 8 to 10 hours before you have the sample taken. You may drink water
5. Go to the location where you are to have a blood sample taken, at the time stated
6. If you are taking any medication, please tell the person who is taking the sample

Fig. 2. Patient preparation for serum Prolactin measurements

#### 4. Specimen sampling and collection

It is important to differentiate between specimen extraction and collection performed by health care staff versus sample collection performed by the patient. When health care professionals are involved the process is easier to control, as these individuals are easily identifiable and accessible through the information provided to the laboratory. The ISO 15189 standard indicates that the specific instructions for extracting and handling samples should be documented and implemented by laboratory management and readily available to the sampling supervisors. The manual for primary sample collection must be part of the quality control documentation. This manual must contain instructions for:

- positive identification of the patient as well as identification, labeling and traceability between the patient, requisition, and primary sample.
- procedures for collecting primary samples, a description of the containers used, necessary additives, type and volume of the primary sample that is to be obtained, the precise time of day that sampling is to be performed, as well as patient position and time of venous occlusion when drawing a venous blood sample. The laboratory must assure that the materials used to perform extractions and collect samples are of adequate quality.
- The identity of the person who collects the primary sample and the date and hour of sample collection must be recorded.
- Safe disposal of the materials used to obtain the samples.

Primary samples that are not adequately identified should not be accepted or processed by the laboratory. When identification of the primary sample is in doubt or if instability in the sample components (cerebrospinal fluid, biopsy) is present, and the primary sample is irreplaceable or critical, the laboratory can opt to process the sample but should withhold the results until the requesting physician or the person in charge of collecting the sample takes responsibility for identifying and accepting the sample; in such cases, this person must sign the request form or the name should be included in the traceability data. If this requirement is not met, the person responsible should be identified on the laboratory report, assuming the analysis is performed.

*Patient or sample identification errors* could have serious consequences affecting clinical decision-making and patient safety; for this reason, these are considered key indicators in the process. Misidentification of the patient or sample can occur at the time of sample collection (the patient from whom the sample is taken does not match the patient listed on the test request form) and also when labeling the sample (a specimen collected from one patient could be mistakenly given a reference number belonging to a different patient).

The Laboratory Accreditation Program of the College of American Pathologists (CAP, 2006) and the Joint Commission on Accreditation of Healthcare Organization (JCAHO, 2007) recommend that all samples sent to laboratories be positively identified during the sample collection process, preferably by two different identifiers. When any doubt exists as to the identity of a specimen, a new specimen must be requested; if this is not possible, the laboratory result should not be disclosed.

##### *Unsuitable specimens for testing*

Most preanalytical errors occur during the sampling process: up to 60% of these errors are attributable to the sample (Lippi et al., 2006a). A retrospective analysis (2001-2005) of results obtained through the Spanish Society of Clinical Chemistry (SEQC) Quality Assessment Program for the preanalytical phase found that the most common preanalytical error was

“sample not received”, followed by “hemolyzed samples” (Alsina et al., 2008). However, now that electronic test requisition requires specific information to be included with each request, including the number and type of containers needed, along with the use of robots to automate this process, the number of not received samples is decreasing. The external quality control programs for preanalytical quality organized by the CAP have found that hemolyzed samples are the most commonly observed errors (Jones et al., 1997).

The main causes of hemolysis during the sample collection process are as follows (Rioja et al., 2009):

- Catheter use; this is one of the factors mentioned in the literature as a cause for the high incidence of hemolysis in hospital units.
- Needle gauge size; a decrease in the needle gauge produces an increase in flow leading to the friction that causes hemolysis. The degree of hemolysis is inversely proportional to the diameter of the needle
- Needle venipuncture and transfer to vacuum tube. Hemolysis is caused by friction in the needle due to excessive pressure in the syringe plunger during extraction or transfer and due to the presence of leaks or poor connections, which leads to turbulent flow
- Venipuncture site. The antecubital fossa is the localization with the lowest incidence of hemolysis. Venipuncture of the hand or forearm increases the incidence rate of hemolysis.
- Antiseptic. Alcohol used as a disinfectant can cause hemolysis.
- Tourniquet duration: applications lasting longer than 1 minute are associated with a greater risk of hemolysis (Saleem et al., 2007).
- Traumatic venipuncture. Venipuncture through hematomas can become contaminated by the hemoglobin released by the tissues. Venipuncture complications, including cannulation difficulties or tearing of the vein, both of which degrade the sample.
- Capillary puncture. This always involves trauma, especially if the area is massaged to produce bleeding. The use of automated capillary puncture devices reduces the degree of hemolysis.
- Type of tube: Larger volume evacuated tubes produce more hemolysis.
- Under-filled vacuum tube. Underfilled vacuum tubes are more likely to undergo hemolysis, especially during transport or centrifugation.
- Excessive or insufficient mixing of the blood and additive (anticoagulant or procoagulant).
- Experience of the personnel who perform the venipuncture.
- Workload. A recent study found that the degree of hemolysis is inversely proportional to the number of extractions performed (Hawkins, 2010)

When analyzing hemolyzed samples, the laboratory must always keep in mind that 3% of in vitro specimens will be hemolytic and this is beyond the laboratory's control (Carraro et al., 2000).

The laboratory must control the process by rejecting all hemolytic specimens that might lead to an incorrect result. Given the high incidence of hemolyzed samples and to facilitate handling of these, in recent years the industry has developed automated systems to detect and quantify the degree of hemolysis.

### *Sample volume*

Laboratories must document and periodically review their requirements regarding sample volume needed to guarantee that neither insufficient nor excessive quantities are extracted.

Estimates have been proposed for the minimum volume necessary for analysis, dead volume required in the analyzers, repetitions, reflex testing, and serum bank (Lippi et al., 2007).

In general, the sample volume collected from patients is insufficiently optimized. A CAP publication on external quality assessment program of sample volumes concluded that tube size has a greater impact on specimen volumes extracted by the laboratory than does the requirements of the autoanalyzer; moreover, this excessive volume, together with the ordering of unnecessary tests, could lead to iatrogenic anemia (Dale & Rudy, 2003).

## 5. Sample transportation

Transportation of samples from the sampling center to the clinical laboratory must meet certain requirements to assure sample stability. The 2009 ADR European norms for highway transport define the packaging requirements for transport of biological samples, which are considered infectious material (Category B). Likewise, the ISO 15189 standard states that the laboratory must monitor the transport of samples to the laboratory so that they arrive within an appropriate time frame and temperature in a manner that safety of all persons involved in transportation is ensured, and in accordance with all national and international regulations.

Neither of these two standards provides specific limits of acceptability regarding transport time or temperature. However, the guidelines published by the National Committee for Clinical Laboratory Standards (NCCLS) H5-A3 in 1994 recommend a maximum of 2 hours for transport of blood samples at a temperature range of 10-22° C. The 2009 GP16-A3 guidelines, also by the NCCLS recommend a maximum of 2 hours and a temperature range of 2-8° C for transport of urine samples.

The main variables to consider during transportation are agitation, light exposure, temperature, transport time, placement of samples within the transport container, type of packaging, and labeling.

Laboratories should document a procedure that specifies the conditions and requirements that must be met during transport in order to properly preserve the samples; in addition, rejection criteria to be used when these conditions are not met should also be defined.

At a minimum, the laboratory should implement the following control mechanisms to assure the quality of this process: control of transport temperature, packaging conditions, and time elapsed from extraction to arrival at the laboratory. Currently, quality control of sample transportation is hindered by a failure to clearly define the limits of sample stability and to register temperature fluctuation during transportation. No indicators are currently available to detect if samples have received excessive light exposure or agitation during transport.

The use of pneumatic tubes to transport samples is somewhat controversial, although most studies have found no significant changes in analytical results. Serum is the sample type most susceptible to hemolysis during transport (Gomez et al., 2009).

## 6. Receiving, handling, and preservation of specimens in the laboratory

The ISO 15189 standards for this preanalytical laboratory process are as follows:

- The primary samples received shall be recorded in an accession book, worksheet, computer or other comparable system.

- The date and time of receipt of samples, as well as the identity of the receiving officer, shall be recorded.
- Criteria shall be developed and documented for acceptance or rejection of primary samples at time of reception. If compromised primary samples are accepted, the final report must indicate the nature of the problem and, if applicable, that caution is required when interpreting the result.
- Always, samples received should be checked.
- If necessary, laboratories should have a documented procedure for the receipt and labeling of primary stat samples.
- Sample aliquots must be traceable to the original primary sample.
- Samples must be stored for a specified period under conditions that ensure the stability of the sample's properties in order to allow test repetition after the initial results have been issued or to carry out additional tests.

### 6.1 Receipt of samples

In this phase, the most important variables for quality control are verification of sample delivery by means of an automatic or manual registration system and verification of the condition of the sample on arrival, to detect and reject samples that are unsuitable for the requested analysis. One key quality indicator in this preanalytical process is the error rate for received samples (sample not sent, coagulated sample, hemolyzed sample, insufficient sample, etc).

A recent review article by G. Lippi et al. (Lippi et al., 2007) provides a series of recommendations to promote, standardize, and harmonize the detection and handling of rejected samples; the general recommendations include staff training, establishment of standardized systems to detect improper samples, and implementation of procedures to detect such samples. Of the specific recommendations given, those of greatest interest are related to the four most common situations in clinical laboratories: how to manage samples with identification errors, samples affected by interferences, coagulated samples, and samples with inadequate volume.

### 6.2 Sample handling

Primary samples cannot always be used directly in the analytical phase but sometimes need to undergo preparation such as centrifugation, aliquoting, or freezing prior to laboratory analysis. Control of all these processes is also fundamental, since errors affecting patient safety can occur, especially during aliquoting and manual identification of each aliquot. The ISO 15189 standard requires that each aliquot be traceable to the original sample. The Joint Commission on Accreditation of Healthcare Organization (JACHO, 2007) and the CAP (CAP, 2006) both advise against manual labeling by laboratory staff.

In recent years, many of the preanalytical processes performed in laboratories have been automated, leading to a considerable reduction in error rates (Da Rin, 2009).

### 6.3 Sample preservation

When samples are delivered to the laboratory, appropriate conditions must be maintained regarding preservation duration, temperature, and light exposure. The time during which a sample can be preserved will depend on its stability, defined as the capacity to maintain the initial value within specific limits for a defined time period. Multiple studies on specimen

stability have been published, some of which have found conflicting results; these discrepancies may be due to the application of different study protocols as well as differing formulas used to calculate stability, and different ways of defining acceptable limits. The SEQC has published two documents to standardize stability studies performed in Spain: one of these proposed a standardized protocol for evaluation of biological stability (Alsina & Gonzalez, 2006a) and the other proposed stability limits derived from biological variation (Alsina & Gonzalez, 2006b)

The laboratory must clearly define stability time and preservation temperatures, and must also regularly monitor refrigerator and freezer temperatures where samples are stored, and also ensure that samples that have been analyzed are not stored longer than the stability limits dictate. Diligent monitoring of sample storage temperatures reduces preanalytical errors and may also prolong the stability time of some samples (Stahl & Brandslund, 2005). The SEQC performed a literature search and compiled the stability limits for several different biological specimens. The CLSI has published a series of guidelines with recommendations for collection, handling, transport, and storage of samples (**Table 1**).

<b>H3-A6:</b> Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard – Sixth Edition. October 2007
<b>M29-A3:</b> Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline – Third Edition (Vol.25, No.10) March 2005
<b>H04-A6:</b> Procedures and Devices for the Collection of Diagnostic Capillary Blood Specimens; Approved Standard – Sixth Edition (Vol.28, No.25) September 2008
<b>C49-A:</b> Analysis of Body Fluids in Clinical Chemistry; Approved Guideline (Vol.27, No.14) April 2007
<b>H56-A:</b> Body Fluid Analysis for Cellular Composition; Approved Guideline (Vol.26, No.26) June 2006
<b>H18-A4:</b> Procedures for the Handling and Processing of Blood Specimens for Common Laboratory Tests; Approved Guideline -- Fourth Edition (Vol.30, No.10) May 2010
<b>GP16-A3:</b> Urinalysis; Approved Guideline – Third Edition (Vol.29, No.4) February 2009
<b>H21-A5:</b> Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays; Approved Guideline – Fifth Edition (Vol.28, No.5) January 2008

Table 1. CLSI Recommendations and Guidelines related with preanalytical phase

## 7. Presence of interferences in the samples

Interferences in samples can be evidenced both in the preanalytical process (visual observation of hemolysis, lipemia, bilirubin), as well as in the analytical (quantification of hemolysis, lipemia, and bilirubin indices) and postanalytical phases (aberrant or unexpected results found during the validation process). However, interferences in the sample should be evaluated during the preanalytical phase since this problem is intrinsic to the sample. The ISO 15189 standard states that the laboratory shall document interferences and cross reactions for each analytical procedure. Other authors (Lippi et al., 2007) also recommend documenting: a) procedures for identifying interferences for each type of specimen, b) the analytical tests affected by the interfering substance, c) the concentration levels at which the interfering substance begins to affect the assay and, d) the laboratory's course of action when an interference is detected.

## 8. Quality assurance for preanalytical processes

When analyzing and comparing the quality control systems used for preanalytical processes to those used in the analytical phase, some fundamental differences become apparent:

1. Analytical quality control systems are much more developed because they were established in the 1950s whereas preanalytical controls were not established until the 1990s.
2. In the analytical phase, processes take place within the laboratory and involve few people; consequently, the variables that need to be monitored are limited and well-defined. The preanalytical phase, in contrast, involves many processes, most of them external to the laboratory; in addition, these processes are quite varied and involve many different people (patients, clinicians, nurses, shippers, administrative personnel, and laboratory staff); as a result, these multiple variables, some difficult to define, must be monitored and managed by each laboratory.
3. The material used to assess quality control in the analytical phase can be assessed much in the same way as patient specimens are evaluated, however this is not the case for preanalytical processes, in which the only option is to establish an error registration system and then calculate the quality indicators.
4. Indicators of quality for analytical processes are expressed as the percent variation for imprecision, systematic error and total error. In contrast, preanalytical quality indicators are expressed as percentages of laboratory activities (including such aspects as number of patients, test requests, quantities, samples, containers, etc), all of which make comparison between laboratories difficult.
5. While quality specifications for analytical processes have been extensively studied and defined by international consensus (Kenny et al., 1999), the same cannot be said for preanalytical processes, as published literature is still incipient and no consensus has yet been reached.

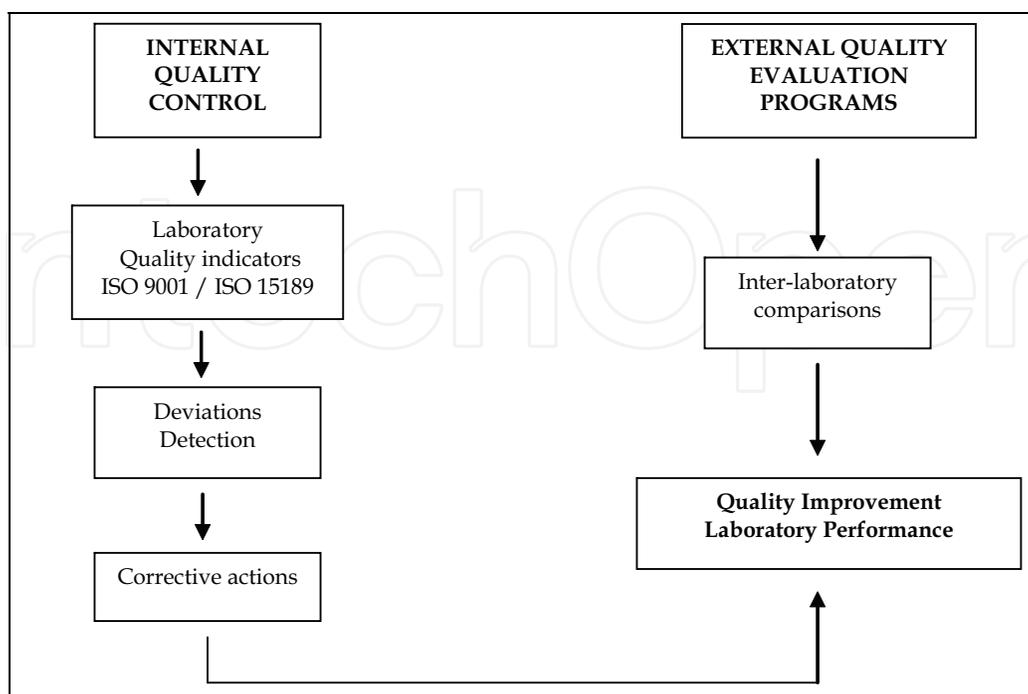


Fig. 3. Quality assurance in preanalytical phase

To attain the same level of quality control that has been developed for the analytical phase, an internal control system for preanalytical processes is needed and also laboratories must participate in external quality assessment programs for these processes (**Figure 3**).

### 8.1 Internal controls

Internal control is based on registering incidents and then calculating the relevant quality indicator for each preanalytical process. The UNE 66175 guide for implementation of indicator systems defines the quality indicator as the data or group of data that help in objectively measuring the evolution of a process or activity. Quality indicators should be designed in such a way as to permit the early detection of deviations from the norm, they must provide information that can be used to continuously improve these processes, and the workload required of the organization to calculate these indicators should be reasonable. The indicators should be updated regularly to adapt to changes in the processes being monitored; in this way, resources are not wasted on indicators for processes that have proven to be stable, but can be focused on processes requiring closer monitoring (CLSI Guideline GP35-P, 2009).

The recommendations given by the Agency for Healthcare Research and Quality and the CLSI can be used for indicator classification. These organizations evaluate laboratory error incidence rates for quality management, including patient safety (Kenny et al., 1999).

Table 2 (Alsina et al., 2007) describes some of the quality indicators currently used for preanalytical processes, as well as the formulas used to calculate them. As shown in table, indicators have not been defined for all preanalytical processes, such as demand for testing, patient preparation, or specimen transport. As it has been said before, the main difficulty in defining and establishing indicators for preanalytical processes lies in the extent of their area of application, which includes aspects involving clinicians as well as patients.

All laboratories must establish quality indicators for the processes that they have the ability to control and monitor over time. It is also important to define the **quality specifications** or limits of acceptability for each indicator; when the results fall outside of these limits, corrective measures should be taken. No international consensus exists as to what the limits of acceptability for preanalytical indicators should be, but recommendations are available for some of these. According to the hierarchical model of analytical quality specifications approved by international consensus in 1999 (**Figure 4**) (Kenny et al., 1999), acceptability limits can be defined by using the results obtained from the top 50% of laboratories in external quality assessment schemes or can be based on current state-of-the-art standards. One example of this would be to use the overall rejection rate obtained by all participants in the SEQC external evaluation program for preanalytical quality over the 2001-2005 period (Alsina et al., 2006c; Alsina et al., 2008), for the following two indicators:

- **Rejected blood samples divided by number of samples: 0.69%**
- **Rejected urine samples divided by number of samples: 2.15%**

Or alternatively, we could use those published in 2002 by the College of American Pathologists (Dale & Ruby, 2003).

- **Rejected blood samples per number of extractions: 0.30%**

The specifications based on state of the art knowledge could be obtained from these sources:

- **Published literature**
- **Results from similar laboratories**
- **Prior data from the same laboratory**

↓	<ul style="list-style-type: none"> <li>• Evaluation of the effect of analytical performance on clinical outcomes in specific clinical settings</li> <li>• Evaluation of the effect of analytical performance on clinical decisions in general</li> <li>• Published professional recommendations</li> <li>• Performance goals set by</li> <li>• Goals based on the current state of the art</li> </ul>
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Fig. 4. Analytical Quality Specifications. Consensus Statement (Stockholm 1999). Scan J Clin Lab Invest 1999; 59: 585

Indicator	Formula
Total incidences in test requests	$100 * \text{n}^{\circ} \text{ of requests with incidents} / \text{n}^{\circ} \text{ of requests}$
Patient data incorrect	$100 * \text{n}^{\circ} \text{ of requests with incorrect data} / \text{n}^{\circ} \text{ of requests}$
Patient data missing	$100 * \text{n}^{\circ} \text{ of request with missing data} / \text{n}^{\circ} \text{ of requests}$
Samples not received	$100 * \text{n}^{\circ} \text{ of each type of sample not received} / \text{n}^{\circ} \text{ of requests}$
Clotted sample	$100 * \text{n}^{\circ} \text{ number of clotted samples for each sample type} / \text{n}^{\circ} \text{ of requests}$
Insufficient sample	$100 * \text{n}^{\circ} \text{ of insufficient samples for each sample type} / \text{n}^{\circ} \text{ of requests}$
Hemolyzed serum sample	$100 * \text{n}^{\circ} \text{ of hemolyzed samples} / \text{n}^{\circ} \text{ of requests}$
Undetected requests with incorrect patient name	$100 * \text{n}^{\circ} \text{ of undetected requests with incorrect patient name} / \text{total n}^{\circ} \text{ of requests with incorrect name}$
Errors in sample management	$100 * \text{n}^{\circ} \text{ sample management errors} / \text{n}^{\circ} \text{ of samples}$
External control exceeds acceptance limits	$100 * \text{n}^{\circ} \text{ constituents exceeding 2 SD of the group using the same method} / \text{n}^{\circ} \text{ data evaluated}$
In-house laboratory reports exceed delivery time	$100 * \text{n}^{\circ} \text{ in-house laboratory reports exceeding delivery time} / \text{n}^{\circ} \text{ reports delivered}$
Reports from referred tests exceed delivery time	$100 * \text{n}^{\circ} \text{ referred test reports exceeding delivery time} / \text{n}^{\circ} \text{ referred tests}$
Copies of reports	$100 * \text{n}^{\circ} \text{ copies sent} / \text{n}^{\circ} \text{ reports}$

Table 2. Formulas used to calculate the indicators

One study of quality indicators for the various preanalytical processes obtained quality specifications by calculating the median result from all participating laboratories. This research was carried out by a group of laboratories whose aim was to obtain state of the art quality specifications for indicators that measure both internal and external laboratory processes for the preanalytical phase (Alsina et al., 2007).

Any laboratory that finds that its results for these indicators do not meet the acceptability limits should take measures to improve the processes. Sometimes, an individual laboratory may encounter practical difficulties applying specifications that have been published by other laboratories or groups of laboratories, a situation that can occur if there are large differences in how errors are defined or quantified or due to inter-laboratory variations in the methods used to measure the variables. In these cases, if the criteria cannot be unified, the best approach is for each laboratory to compare its own results over time. The results of this study are similar to those reported by similar studies.

- Thus, for the overall indicator of the number of erroneous samples divided by total requests, the result in this group was 5% versus 4.6% reported by Romero and colleagues (Romero et al., 2005).
- The indicator of incorrect samples per number of samples is 2.3(%), (Romero et al., 2005) similar to the 2% rate reported by Plebani (Plebani, 1997).
- The indicators for sample not received (2.9%), hemolyzed sample (0.8%), and coagulated sample (0.55%) are also similar to the results reported by Lippi et al (Lippi et al., 2006b).

Therefore, we can deduce that the quality specifications proposed by Alsina (Alsina et al., 2007) reflect current state of the art and support the recommended acceptability limits.

The same group of laboratories carried out a follow-up study (Llopis et al., 2010) in which quality specifications for the preanalytical indicators were assessed annually over a 5-year period following their initial implementation in order to evaluate changes (Alsina et al., 2007) The authors proposed converting the specification value to the six-sigma scale in order to establish the degree of control over the process, with processes having a sigma greater than or equal to 4 considered well-controlled (Westgard, 2006). Most of the indicator values remained stable over the 5-year study period and so the mean of the inter-laboratory medians—which proved to be a robust value over the course of the study period—was recommended as a desirable specification. However, for indicators that showed a clear improvement over this period, the authors recommend that the specification be defined as the current median because changes introduced in the processes show that more demanding specifications are achievable. The research group believes that the proposed specification for processes with a sigma of 4 or less should be considered provisional because such processes need to be improved. In addition, for processes that have an important impact on patient safety (sentinel event indicator), the group recommends a specification of zero (0%). Though this value may seem unattainable, all necessary resources should be dedicated to eliminating these types of incidents, example of which include test requisitions containing incorrect patient demographic information or poorly labeled samples.

The proposed quality specifications for some of these indicators are described below:

**Indicators for preanalytical processes external to the laboratory:**

- *Total errors in analytical requests* (relation to total requests received): a provisional specification of 3.4% (sigma 3.4) is proposed.
- *Requests with incorrect patient demographic data*: even though the error rate in the study was only 0.11% (sigma 4.6), a specification of 0% is recommended given the importance of this indicator (sentinel event).

- *Sample not received*: the proposed specification is 0.5% of all samples. Early morning urine is the sample with the highest incidence rate, with an average median of 1.7% and a sigma of 3.7, which indicates that this process needs improvement. The other samples (serum, EDTA, citrate, 24 hours urine) have median values below 0.5% and sigma metrics ranging from 4.1 to 5.1, which reflects, in general, a process that is well under control.
- *Coagulated samples and insufficient samples*: a value of 0.1% is proposed as the specification for both indicators because the sigma ranges from 4.3 to 5.0.
- *Hemolyzed samples*: this indicator largely depends on the method used to detect hemolysis (visual vs. spectrometric), and the recommended provisional specification is 0.6% (equivalent to sigma of 4.1).

Among those indicators that indicate sample quality, the most significant are “hemolyzed sample” and “sample not submitted”, although the use of computerized test requisition that includes instructions for sample pick-up will improve this indicator. The existence of various methods for detecting hemolyzed samples together with the use of varying sample rejection criteria makes it difficult to obtain robust state of the art specifications for this indicator (Gomez et al., 2009; Lippi et al., 2009).

#### **Indicators for preanalytical processes within the laboratory:**

- *Failure to detect patients with incorrect demographic data*. Even though the error rate for this indicator was quite low (0.11%; sigma 4.6), the recommended specification is 0% because this is an indicator for a potential sentinel event.
- *Errors during sample handling*. The proposed specification for this indicator is 0.03%, which is equivalent to a sigma of 5.0.

These results tell us that once the most appropriate indicators have been established for each preanalytical process and quality specifications for these defined, it will be important to calculate the indicators and evaluate their efficacy on a regular basis. In this way, improvements can be made in any process that fails to meet the defined acceptability limits.

#### **External quality evaluation programs for preanalytical processes**

External assessment programs based on inter-laboratory comparison are used to evaluate each participating laboratory in comparison with the others. Statistical analysis is used to evaluate the data provided by participating laboratories, such as the number of errors that occur in the preanalytical phase, and the results of the analysis are then sent to each participating laboratory. As a result, each laboratory can view its own results and, if necessary, take actions to improve processes found to be below standard.

These external review programs also typically provide recommendations on how processes can be improved, as well as they inform the laboratory as to the most appropriate indicators to use for each process. They can also help to establish quality specifications.

One of the greatest difficulties in statistical analysis of the data in external evaluation programs is a lack of standardization in the data collection process. Data registration in many laboratories is performed manually rather than by computer, meaning that this activity is personnel-dependent. Indicator calculation has not been standardized because there is no consensus on how the error rates should be calculated (with respect to number of patients, number of samples, number of requests, number of extractions, etc.). Other additional difficulties are that many laboratories lack experience with external review programs and, moreover, relatively few external assessment programs for the preanalytical phase are available, and even those that are available only evaluate a limited number of processes.

In 1989, the College of American Pathologists (CAP) became the first organization to carry out these types of review programs in the United States (Q Probes), and the CAP publishes its findings on a regular basis. Each study evaluates several different variables both in the preanalytical phase (identification errors in the laboratory, specimen collection volumes, accuracy of send-out-test ordering), and in the postanalytical phase (clinician and nursing satisfaction surveys, notification of critical values), and each year the variables studied are changed (Dale & Novis, 2002; Valenstein et al., 2006; Zarbo & Jones, 2002).

The SEQC (Spanish Society of Clinical Biochemistry) began a quality assurance program for the preanalytical phase in the year 2000. The salient features of the program include: anonymous participation, rigorous confidentiality, quarterly evaluation (blood and urine samples, each sent twice yearly), computerized data processing, and a duration of one calendar year. The main objective of the program is to determine the current state of quality for the preanalytical phase in clinical laboratories in Spain by quantifying the number of specimens rejected by each laboratory compared to the number of rejections in all participating laboratories.

In this program a certain number of rejections are registered (the first 100 for blood samples and the first 50 for urine samples) or the maximum number of rejections registered in one-month period. A rejection is defined as the inability of the laboratory to provide results to the clinician for one or several test requests due to causes attributable to preanalytical error.

Currently, this program only measures quality for three preanalytical processes: blood sample collection performed by health care personnel, urine sample collection/pick-up by either patient or health professionals, or transport of samples.

The assessed indicators are:

- Coagulated sample
- Sample not sent
- Insufficient sample
- Hemolyzed sample
- Unsuitable sample
- Unidentified sample
- Defective transportation
- Insufficient sample relative to anticoagulant quantity
- Contaminated sample
- Other

For each assessment, the participating laboratory is required to send the following data:

- General laboratory characteristics: hospital or primary care, public or private, etc.
- Rejection registry and characteristics of these rejections (urgent or programmed request, permanent or temporary staff)
- Laboratory activity: number of requests, number of extractions and number of samples of each type during the study period.
- Characteristics of the laboratories compared to sample collection centers: person responsible for preanalytical phase, coordinator of the off-site sample collection center, criteria for sample rejection, internal quality control of the preanalytical phase, documented extraction procedures, what information (a computerized list, sample labels or instructions on the request forms) is given to staff about the type of samples to be extracted, training of collecting personnel, and existence of off-site collection centers.

- Supplementary data, type of requests (urgent or programmed) and type of personnel (permanent staff or not).

The organizers of the program collect all the information provided by the participating laboratories, carry out statistical analysis of the data, and inform each participating laboratory of the rejection rate for the total number of samples and the type of samples obtained from each laboratory, as well as the total rejection rate by type of sample for all participating laboratories. A general report of the group data is sent to all participating laboratories. This report includes data from all participating laboratories and includes the rejection rate distribution for all participants, correlation between rejection rate and the predefined characteristics for each participant and the multiple regression analysis of the rejection rate compared to the aforementioned characteristics.

The results obtained over the 5-year period since these programs were initiated show an overall blood sample rejection rate of 0.69 % (Alsina et al., 2008), with the highest rejection rates for sodium citrate ESR and coagulation samples, where the main cause of rejection was given as "sample not received". However, for serum and plasma-heparin samples, the main cause of rejection was hemolysis. Variables related to the organization of the preanalytical phase that have a significant impact on rejection rate have also been evaluated: a positive association was found between the rejection rate and the presence of off-site collection centers, while the presence of a collection coordinator, daily registration of incidents, and regular meetings with collecting supervisors were all negatively correlated. As for the type of contract of the collection personnel, permanent staff obtained a 0.58% rejection rate versus 0.95 % for temporary staff. The heading "non-permanent staff" includes all personnel who are hired on a temporary basis or rotating basis.

In terms of recent urine samples (Alsina et al., 2006c), the overall rejection rate of 2.16 % is much higher than that for blood samples in the same period (0.69%), with the most common cause of rejection being "urine sample not sent" (81.6%), which was also much higher than in the case of blood samples (37.5 %).

The organizational management that the laboratory brings to off-site collection centers could help to minimize the risk of error that occurs in this phase. Simplification of the entire process, computerization, and robotics are all potential preventative measures for those processes involving a higher risk of compromising patient safety (Table 3)

RISK OF ERROR	PREVENTIVE ACTION
Incorrect identification of the patient	Process Automation
Analytical Request Errors	Computerized test requesting
Remaining Samples	Indicate exactly the number of samples per request
Misidentification samples	Automate samples labelling
Incorrect Sampling	Quality materials Information and training

Table 3. Measures to minimize the risk of error that occurs in preanalytical phase

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The rich palette of topics set out in this book provides a sufficiently broad overview of the developments in the field of quality control. By providing detailed information on various aspects of quality control, this book can serve as a basis for starting interdisciplinary cooperation, which has increasingly become an integral part of scientific and applied research.

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