The Scope, Quality and Safety Requirements of Drug Abuse Testing

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SUMMARY

The aim of this review is to provide information and updates on the scope and requirements of drug abuse testing.

Drug abuse testing is one most important tools for determination of drug use. It must fulfill the quality and safety requirements in judgmental, legal, and administrative decisions. Furthermore, it must meet additional requirements such as selection of the appropriate test matrix, appropriate screening test panel, sampling in detection window, obtaining individual consent, identification of the donor, appropriate collection site, sample collection under observation, identification and control of the sample, reliable material and instrument use, and specimen custody chain in the preanalytical phase. In the analytical phase; the analysis in authorized and audited laboratories, specimen validity tests, the reliable testing methods, the strict quality control and assurance, and two-step analysis must be performed. The storage of the split specimen, confirmation of the split specimen in case of objection, result custody chain, the appropriate cut-off concentration, and the appropriate interpretation of the results in postanalytical phase must be duly recognized.

The workflow and analytical processes of drug abuse testing has been explained in last posted regulation from the Department of Medical Laboratory Services, Ministry of Health in Turkey. Physicians must know and apply the quality and safety requirements in drug abuse testing according to these regulations that were recently assembled in Turkey.

Keywords: Substance abuse, clinical chemistry tests, government regulation

INTRODUCTION

Drug abuse is an important public health and safety problem, and the war on drugs has become a global priority. Drug abuse testing has been a gold standard for determining drug use and is an intregral part in combatting drugs abuse (Gerson and Subramaniam 1998, MacDonald and Wells 1994, Wish and Gropper 1990).

After the legal arrangement on probation services in Turkey, regulation of drug abuse testing to meet the quality and safety requirements for legal and administrative needs in health institutions was deemed mandatory (Regulation of Probation Services 2005). However, these regulations did not start until 2011, which was after the Ministry of Health Medical Laboratory Services Department was established (Decree on the Organization and Duties of the Ministry of Health and its Affiliates 2011).

The Medical Laboratory Services Department first defined quality requirements of medical laboratory services in Turkey, and then started to audit and give authorization according to these general laboratory requirements. Article 12 of the Medical Laboratory Regulations states that "the working procedures and principles of medical laboratories for illicit and abused drug testing are identified by the Ministry of Health"

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(Medical Laboratories Regulation 2013). In the context of the Medical Laboratory Regulations and the final tasks of the National Action Plan for Combating Drugs (The National Strategy of War on Drugs 2016), the Ministry of Health issued two circulars and created legislation related to laboratory services in drug abuse testing. The first circular was issued for Medical Laboratories executing drug screening (Circular on the Working Procedures and Principles that Medical Laboratories that make Illegal and Abused Drug and Substance Analysis and Medical Laboratories at Substance Abuse Diagnosis and Treatment Centers 2014). This regulation defines the quality requirements for drug screening testing to be applied in medical laboratories. It has been reported that these quality requirements will be checked both during the establishment and authorization (licensing) and also at the time of inspection. The medical laboratories that apply drug screening in health institutions, which include the Alcohol and Drug Addiction Treatment and Research Center (AMATEM), the Child and Adolescent Drug Addiction Treatment Center (CEMATEM) and Probation Policlinics, have been inspected annually according to these special requirements since 2014. The second circular was issued for the medical laboratories executing drug confirmation testing (Circular on the Working Procedures and Principles of Confirmaion Laboratories that make Illegal and Abused Drug and Substance Analysis in Urine Samples 2015). Regarding this, The Ministry of Health announced the special requirements for national drug confirmation laboratories. It has been announced that the drug confirmation laboratories of nine major cities, including Adana, Ankara, Antalya, Diyarbakir, Erzurum, Istanbul, Izmir, Kayseri and Samsun, will be authorized. They will be licensed according to the Medical Laboratory Regulations and will be obliged to meet the special requirements. In the second half of 2016, two institutions from Ankara (Hacettepe University Faculty of Medicine and Gülhane Education and Research Hospital) were authorized as drug confirmation laboratories. The laboratories from the other eight cities will apply and medical laboratories will be authorized after evaluation and approval. In December 2016, the Ministry of Health also issued a guideline on drug screening, which detailed the workflow and analysis processes for drug abuse testing (The Principles of Operation of Medical Laboratories and the Medical Laboratories at the Substance Abuse Diagnosis and Treatment Centers that Makes Illegal and Abused Drug and Substance Analysis in Urine Samples 2016).

An effective drug abuse testing plan can be applied with a good understanding of the scope and requirements. For this purpose, various sources of information are being created in Turkey for laboratorians (Küme et al. 2009, Kara Uzun et al. 2015, Küme et al. 2016, Kara Uzun et al. 2016). This aim of this article is to provide information and updates for clinicians on the scope and requirements of drug abuse testing.

The Scopes of Drug Abuse Testing

The determination of drug use: The term "drug" is often used for molecules that cause drug use disorders such as abuse or addiction due to psychoactive effects. Drug use causes biological problems such as delirium, dementia, intoxication, withdrawal, risk of biosecurity, fetal anomaly; psychological problems such as mood disorder, anxiety disorder, sleep disorder, psychotic disorder, adjustment disorder and social problems such as accidental risks, suicidal tendency, and economic loss (American Psychiatric Association 2013). The production, sale, and use of drugs is legally restricted and/or prohibited in Turkey similar to the rest of the world, which is on the grounds that it is a serious public health and safety problem (Turkish Penal Code 2004). In this respect, the determination of 'drug use' is necessary for legal purposes.

Different tools are used for determination of drug use (Normand et al. 1994). These are: (1) Drug user characteristics: The personal characteristics of the user, such as age, clothing style, lifestyle, friend choice, family characteristics, music choice, relationship style, speech and word choice, are indicators that are difficult to distinguish from early onset drug use. Because it is similar to puberty or stress, it reflects low specificity and sensitivity. (2) Drug use findings: An inidicator of acute intoxication and withdrawal is higher specificity and sensitivity. Drug use findings are made up of various tests that are applied in the field and used to determine if the drug effects a person. There are standardization problems because these tests differ according to the application. Some tests such as walk and turn test, horizontal gaze nystagmus test, and one leg stand test are more standardized than other test including the hand flick test, finger count test, and finger nose test. (3) Diagnostic scales: The Addictive Severity Assessment Test (ASI), which identifies and classifies drug abuse characteristics and the tests for specific substances (such as the Michigan Alcoholism Screening Test) are used for screening, diagnosis, referral, and follow-up of people with drug abused. (4) -Laboratory tests: one of the most important tools for determining drug use. Laboratory tests are the only tool that can be used as an objective evidence, especially for the process of making critical legal and administrative decisions. These can help identify the specific molecules present in the body.

There are several objectives in practice to determine drug use. These are: (1) Determination of the last drug use: This is applied to suspected individuals or persons under risk of use. (2) Identifying chronic drug users: identifying individuals with a drug use disorder and how to direct the individual for treatment. (3) Individual drug monitoring and discouraging: The individual's drug abuse tendency and frequency are monitored. The goal is also to prevent drug abuse. (4) Community drug monitoring and discouraging: The tendency and frequency of drug use in the society is monitored. National and regional substance use profiles are identified. The aim here is

to prevent drug abuse by inhibiting the use of the drug socially (Wish and Gropper 1990, Report of the Task Force on Youth Drug Abuse 2008) .

Determination of drug use is a decision guide for medical, legal, or administrative practice (Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs 2005). Proving the use for medical purposes is vital for diagnosis and treatment. For legal purposes, it can affect the individual's rights and freedom. Proving the use of drug administrative purposes can affect the individual's work and social situation in administrative practices (such as workplace employees, students, and sports events). Certain quality and safety requirements must be met for drug abuse testing to be used as evidence in legal or administrative practice.

The application of drug abuse testing: Drug abuse tests are applied to determine drug use for the purpose of combating disease, crime, or substance. Drug fighting programs are established to combat drug use disorders more effectively. Various programs can be applied to drivers in the case of license applications for individual or public transportation, to the students in schools, to the sportsmen in competition, and to employees in workplace. There are five basic components of a successful program of drug control: (1) Establishment of the program policy, (2) Training of practitioners, (3) Consciousness of the people involved, (4) Drug abuse testing, (5) Addiction counseling and treatment possibilities (Walsh 2008, Wish and Gropper 1990). Drug abuse testing is the most critical step in the program of drug control, since it is the decision maker. For this reason, it should be supported by the quality and safety elements that are mentioned below.

Drug abuse testing has been applied for three purposes in various areas. These are: (1) Medical: Drug abuse test results are used for diagnosis and treatment of disease. This area is called "clinical toxicology". They are applied in areas such as drug counseling (emergency room, anesthesiology intensive care unit etc.), follow-up of addiction treatment (Addiction treatment centers, psychiatry, child psychiatry service etc.), or pain therapy (neurology, oncology, anesthesia service etc.). (2) Forensic (Legal): It has been used to fight crime and to obtain evidence or determine criminal charges. This area is called "forensic toxicology". It can be applied to areas such as supervised freedom (according to the Probation Law), motor vehicle driver (according to the Road Traffic Law) and child abuse, sexual assault, and armed attack (according to the Turkish Penal Code). (3) Administrative: It has been used to combat addiction in order to detect early and direct treatment. It has been applied for purposes such as screening at the workplace, screening athletes at competition, or scanning teenagers at school. This area has been termed "workplace or behavioral toxicology" (DuPont and Shea 2013, Lum and Mushlin 2004).

In general, the production, sale, and use of the drugs is illegal. In addition, there is always the potential that drug use transforms to legal cases directed to harming the fetus in pregnancy, causing injury, or fatal accident, workplace accidents that can be the subject of monitary and compensatory litigation. For these reasons, it is always possible to come across legal processes for drug abuse testing. Because no evidence can be obtained retrospectively for individual victims and likewise legal responsibility concerning employees, it has been recommended that legal proceedings be carried out on all drug abuse testing cases (TDM8-A: Urine drug testing in the clinical laboratory Approved guideline 1999). In the past and now, health institutions send specimens very carefully to the Forensic Medicine Laboratories according to the Regulation on Forensic Medicine Institutions in Turkey (Regulation on Forensic Medicine Institutions 2004). Moreover, the units in health institutions must send drug abuse specimens to the medical laboratories according to last drug abuse testing legislation of Ministry of Health in Turkey (The Principles of Operation of Medical Laboratories and the Medical Laboratories at the Substance Abuse Diagnosis and Treatment Centers that Makes Illegal and Abused Drug and Substance Analysis in Urine Samples 2016).

Laboratory test results are used in medical decisions such as diagnosis, treatment, or follow-up finding. Therefore, it is desirable to have sufficient analytical specificity (ability to measure a specified search only) for differential diagnosis, adequate analytical sensitivity for early diagnosis (ability to respond precisely to a change in concentration), or sufficient analytical precision (ability to produce close values in repeated measures) for successive measurements. The screening tests should have high analytical sensitivity for early diagnosis of drug use. If drug abuse test results are used as evidence of crime in legal decision or as evidence of behavior/performance in administrative decision, it must have high analytical specificity. The performance of screening tests are not sufficient for legal accusation. The drug molecule should definitely and unwaveringly be defined by confirmation methods. Hence drug abuse testing results may led to punishment (legal consequences), affect business and professional life (financial consequences), and affect family and/or friends relations (social consequences). For this reason, a two-step analysis strategy has been used for drug abuse testing in today's conditions. Drug screening tests in the first step and confirmation tests for positive samples in the second step have been applied.

The Quality and Safety Requirements of Drug Abuse Testing

If drug abuse testing is used for legal or administrative decisions, it must meet certain quality and safety requirements. These requirements are summarized in Table 1 and are described below.

Table 1. Quality and safety requirements of drug abuse testing

Preanalytical phase
Selection of the appropriate test matrix
The appropriate screening test panel
Sampling in detection window
Obtaining individual consent
Identification of the donor
The appropriate collection site
Sample collection under observation
Identification and control of the sample
Reliable material and instrument use
Specimen custody chain
Analytical phase
Analysis in authorized and audited laboratories
Specimen validity tests
The reliable testing methods
The strict quality control and assurance
Two-step analysis
Postanalytical phase
The storage of the split specimen
Confirmation of the split specimen in case of objection
The appropriate test result report
Result custody chain
The appropriate cut-off concentration
The appropriate interpretation of the results

The selection of the appropriate test matrix: Urine specimens are often used and especially preferred in workplace drug screenings as a standard sample type. The drugs and/or their metabolites collected from urine can be identified in high concentrations due to urinary excretion of toxic substances. Urine specimens are the most preferred sample type in drug abuse testing due to their distinct advantages such as period of drug detection window, noninvasiveness, and sufficient sample volume is easily collected and adapted to point of care testing (Wong and Tse 2005). Alternative samples can be used in drug abuse testing. Several samples such as blood, hair, nail, oral fluid and rarely sweat, meconium, amniotic fluid, breast milk, and tissue samples have been routinely used. Alternative sample types can be used by evaluating the pros and cons according to the application requirements. For example, meconium specimens are preferred in newborns as an intrauterine exposure indicator. In addition, blood specimens can be used as an indicator of intoxication of a received dosage or monitor the excretion, while hair or nail specimens are preferred for longer periods of a drug detection window. Lastly, oral fluid on crime scene setting is also a point of care testing (Barbarajean et al. 2012, Caplan and Goldberger 2001).

There are a number of issues that need to be considered when using alternative samples for determining drug use. The first is the applicability of the analysis. Although the importance for improvement are increasing, the number of laboratories routinely used for drug abuse testing in alternative samples are very low in Turkey due to cost and procedure difficulties (Gallardo and Queiroz 2008). The Forensic Medicine Institution in Turkey applies drug abuse testing in alternative sample types such as hair (nail if necessary), but do not accept specimens other than the ones requested by the judicial authorities. The second is the differences in total laboratory processes (Caplan and Goldberger 2001). The detection windows can vary dependent on the sample type. A specific sampling procedure should be applied to each sample type. For example, blood should be taken by a standard venous route, hair by cutting from the bottom of the hair nape region, and oral fluid by a special sample collection apparatus into appropriate containers. The reagent kits must be produced for the sample type to be analyzed. It must be validated or verified for that sample type before use. The matrix of quality control and calibrator materials should be similar to the sample type to be analyzed. The result should be evaluated according to the sample type specific cut-off concentrations.

The sample type used in drug abuse testing applied in intoxications is important. The concentration of drug detected in urine specimen is not correlated with the dose and effect of the substance taken. Therefore, the use of the urine sample for medical purposes such as monitoring detoxification is not beneficial. However, the use of blood and oral fluid sample types is more useful for medical purposes (Hammett-Stabler et al. 2002).

The appropriate screening test panel: The physician may request a single test for control or monitoring purposes. However, testing for a single drug is not appropriate because of the use of a wide variety of drugs and the possibility that a person can use more than one drug at the same time. Technology is insufficient to scan hundreds of substances at the same time. For reasons stated above, the analysis of all possible drugs is not possible in today's conditions. Generally, a minimum test panel containing the most commonly used drugs is established to determine drug use. This test panel is generally determined by the health authorities and it is mandatory. In addition, the health institution may also create an extended test panel by adding tests for additional drugs to cover their own needs and to include the regional drug use profile. As the needs change, it is recommended to update the tests at certain intervals (ideally once a year) (DuPont and Shea 2013). Physicians may add new tests in their institutional laboratory screening test panel.

The drug test parameters are determined according to the needs of the application purpose. Scientific guidelines such as medical literature for medical needs, legal regulations for judicial needs, and administrative regulations for social needs are used as information source. For example, a test panel containing cocaine, opiates, barbiturates, amphetamines, propoxyphene, phencyclidine and tricyclic antidepressants was proposed for test requests made with doubt on poisoned patients in the emergency department in the "National Academy of Clinical Biochemistry" guide published in America (Wu et al. 2003).

Such test panels are beneficial for providing early intervention to the patient and quickly making a diagnosis for the medical condition. Legal (depending on the country) and administrative (depending on the institution) regulations may require the application of different test panels for needs, respectively.

There are two exceptional situations for the parameters measured. (1) Measurement of the drug as the parent molecule or metabolite: Drugs absorbed by the body excrete unchanged chemical structure as parent molecule or changed chemical structure as metabolites. Metabolites have a larger period of detection window because their half-life is longer than their parent molecules. Each drug forms a specific analyte pattern that contains the parent molecule and/or its metabolites in a specific order relative to each other in different sample types. For example, urine samples contains more metabolites, while blood and oral fluid samples contain more of the parent molecule. Urine sample is also regarded as the standard sample for having a relatively larger analytical pattern and higher analyte concentration. Care should be taken in drug abuse testing for metabolites, because some metabolites can be excreted as an unmetabolized parent molecule or as contaminated with the parent molecule. (2) Measurement of the drug as a single or group: Immunochemical methods used in screening measure both the parent drug and metabolites of drugs by epitope recognition, while chromatographic methods used in confirmation measure each parent molecule or metabolite separately (Report of the Task Force on Youth Drug Abuse 2008).

The sampling in detection window: The detection window is the period that the parent molecule and/or its metabolites can be detected on the specimen. The detection window starts after exceeding cut-off concentration (early detection point) and ends after deceeding cut-off concentration (late detection point). This period can be effected from many factors. This variability can also cause difficulties in determining the drug use, as it causes the test to be negative. The detection window varies depending on the drug. In addition, the pharmacokinetics of the drug (affected by many factors related to the drug and human), the test method, the sample type and the cut-off concentration are important (Vandevenne et al. 2000, Verstraete 2004).

In drug abuse testing, administrative cut-off concentrations for urine samples were selected so that they could be detected during weekday analysis (at least 2-4 days) after the employee's drug use on the weekend. The detection windows are usually 2-4 days for hydrophilic drugs (such as amphetamines, opiates, cocaine). However, lipophilic substances (such as cannabis) can be detected at 2-7 days for single use - even up to 1 month for continuous use. For this reason, a drug test should be requested after 1 month of starting probation or addiction treatment for lipophilic drugs (Cary 2006).

The detection window is not usually considered for determination of drug use at the event. However, it can be retrospectively evaluated after negative results.

Obtaining individual consent: The sample collection should be considered as proof in this testing. Sample collection is an intervention to the integrity of the body, and it can not be applied legally without individual consent and permission (Turkish Penal Code 2004). For this reason, drug abuse testing should not be done without individual consent. Furthermore, the privacy of the human body is respected and the individual must be protected during the sample collection in our culture. Otherwise, the person may rightfully refuse to give the sample and may not be able to express his anxiousness. In this case, the situation must be understood and conditions must be corrected. Sometimes the individual does not accept to give a sample because of the positive result due to expected possible drug use. In this case, the sample should not be insisted on being taken and must be reported to the physician and probation office (İpekcioğlu 2014). Alternatively in some situations, it may be possible to take samples without official approval by the judicial authorities request or in case of medically necessary circumstances (Warner et al. 2003). It is also not appropriate to process samples taken by parents without the consent of the child or teenager. Such behavior prevent trust-seeking and professional assistance (Levy et al. 2014).

The identification of the donor: The identity of the person should be proven with a photo identity (ID) card. Photocopies of ID card or ID card without photos should not be accepted, and a photo ID card should allow easy recognition. In order to prevent ID fraud, the ID card should be laminated and cold stamped. In the event of suspected fraud on the ID card (such as the torn lamination, alteration of the photograph, deletion of the text), a new identity must be requested.

The appropriate collection site: The sample collection area should provide features hygienic excreation and avoid possible cheatings. These are: (1) Non-chaotic toilet: The toilets should be not be in a crowded or chaotic place (not a passage corridor, a dead-end corridor is ideal). (2) Reserved toilet: The toilet should be used only for drug abuse testing; If this is not possible, public use should be prohibited during this process (such as restricting use at certain times or days). A gender private toilet is ideal. However, if this is not possible a single toilet can be used in turn. Unauthorized access to the sample collection area should be avoided; therefore, the public toilets are not suitable for drug abuse testing. (3) Emptied toilet: All material that may be a possible cheating tool in the toilet should be removed (brush, towel, towel box, sink, trash box, bucket, table, temperature gauge, excess sample container, label, and paper, etc); ideally it should be completely empty. Apart from the specimen collection, there should be no other applications such as specimen acceptance, temperature measurement, document signing, etc. in the toilet. (4) No water

contained toilet: The water sources should be closed or the identified blue paint should be for any water source. These applications can be applied where access to the reservoir is stopped by sealing or burying in the wall. Hand hygiene with a wet napkin can be provided. (5) Observable toilet: Facilities should include lighting and mirror setup for adequate observation. The mirror setup should be properly positioned and wide enough to allow comfortable viewing from the back of person. (6) Hygienic toilet: Opportunity for hygienic hand washing, appropriate toilet cleaning, and adequate ventilation for odor problems should be provided. It is also recommended that the person have the option of a safe and hygienic place to remove extra outfits and leave their bags, clothes, and other items.

Sample collection under observation: Interventions to manipulate the test results for drug abuse is called cheating. A wide variety of manipulations can be made in various sample types and laboratory arrangements. The five most often ways to cheat for urine specimens are: (1) Changing the person: The specimen is collected from another clean person, (2) Changing the specimen: The previously taken clean urine of his own of other animals or lyophilized commercial products are used, (3) Diluting the specimen: ingestion of some substances that increase oral fluid intake, drug excretion, or elimination (such as Gold Seal ®, Clean 'n Clear ®, Test-Free ®, Naturally Klean ®), diuretic intake or adding fluid outside to the urine. (4)Adding the cheat: interference substances (such as vinegar and bleach, soap-like cleansing products) or ingestion of interference substances (such as aspirin, niacin, zinc sulfate, Puri-Blend ®, TheStuff ®). (5)-Changing the result: The test results can be change by entering the information system of authorized or unauthorized persons. Cheating most commonly occurs in the specimen collection step. Unobserved urine specimen collection is open to intervention and can easily be manipulated during specimen collection. For this reason, the specimen should be taken under observation.

The urine samples can be taken in three ways: (1) Specimen collection without observation: Depending on the decision of the physician making the test (especially for medical purposes), standard sample collection procedures can be performed without observation. In this case, the patient or his/her relatives are informed of the result and this can not be used for judicial or administrative purposes. In addition, sample collection without observation should be noted by the physician as a written note. (2) Specimen collection with direct observation: The observation is applied directly face to face. Urine sample is monitored from sexual organs to collection container. The privacy of the person is not considered. It can be applied in high discipline (like soldiers, police) and in high competition conditions (such as international competitions, doping scan). If done properly, there is no possibility of cheating. (3) Specimen collection with indirect observation: The observation is indirectly applied from the back or side of the person by mirrors. The privacy of the person is protected, therefore it is a more humanist application. The suspicious acts of the person can be monitored and, though there is the possibility of cheating, it is a deterrent against manipulating.

Alternative sample type (such as blood, hair, and intraoral fluid) is usually taken by health care professionals with special techniques, so no further observation is required. However, witnesses may be available.

During specimen collection with observation, self-protection measures must be taken for the risk of physical assault, theft and infection, and specimen collection must be witnessed. For this reason, it is ideal that there are two observation officers for witnessing and protecting of each other. If these conditions are not met, at least one person should be at specimen collection observation. It would be appropriate to provide observation facilities with two people to help disabled persons. The gender of the observation officer should be appropriate for the patient and he/she should be appointed duty times. A fixed observation officer is not suitable as it may be subject to threat or bribery proposals. The observation officers should be changed constantly from the institution personel pool. Observation officers are determined by the patient's profile and the capabilities of institution facilities. Security personnel or even law enforcement officers can be assigned for risky persons apt to attack or cheat. In the safer conditions, various personnel can be utilized.

If the patient is apt cheat frequently during specimen collection, taking unannounced samples, taking multiple samples (which are not known to be analyzed), or taking alternative sample types can be implemented as counter measures against it. In addition, there are other measures to re-sample and re-analyze from the split sample used in case of suspicion.

Identification and control of the sample: Barcode labels that are used for sample identification should not easily break and be torn. It should be adhered to the container closure and to the chamber seperately. It must have the necessary information. The ID and the information in the label must match. Ideally, seal labels should be affixed to the sample lid to prevent tampering.

After the sample is delivered, the properties of the urine (quantity, temperature, and appearance, etc.) are checked for acceptability. Sample acceptance and rejection criteria for analysis and tampering should be determined. Before giving the sample, the person should also be notified.

Reliable material and instrument use: Some different critical materials and instruments are used in drug abuse testing. The processes of selection, purchase, ordering, acceptance, installation, use and storage of these materials, and instruments

must be well planned due to required proper results of drug abuse testing.

Each material and instrument to be used in drug abuse testing should have the technical characteristics to meet the required quality and safety requirements. Some of these are: (1) Sample containers: It must be wide-mouthed so that it can be collected while urinating. Ideally, it should be made of sterile and chemically inert material to avoid contaminating the assay. The volume should be graduated to measure the amount of urine collected. They must have a seal label to indicate tampering. The closure should be resistant to opening and should be closed with two clicks. (2) Transport bags: There must be separate sections for blood and urine transport. It must be manufactured from material that will prevent it from being affected by the pulleys and provide thermal insulation (it should be able to carry cold chain between 8-15 ° C for up to 24 hours with an ice cube). The cover of the bag should be able to be locked (ideally a single-use lock). It should be suitable for cleaning with disinfectants. "Sample Transport Bag" must be written on it. (3) Temperature measuring devices: Measurements should be made with the specified technical criteria. The devices used should be evaluated for risks of contamination (due to immersion), safety (due to sample container opening), and erroneous measurement (due to lack of proper technique). (4) Strips for sample integrity: Measurements should be made with the specified technical criteria. It must be protected from the open air for humidity affects.

The specimen custody chain: Precautions should be taken to ensure the safety and validity of the samples to be used as evidence. All processes are applied with an authorized person and by hand. In addition, they must be recorded in written and signed form. For this, a registration form must be created to include all the steps from the beginning to the end of the process.

To prevent tampering of the sample during sample transfer stage, close transfer distances (sampling unit and laboratory sample acceptance unit at the same place) should be done with authorized personnel, sealed urine containers should be used, and unauthorized entry into the laboratory should be prevented. In the case of long distances transfer (the sampling unit and the laboratory sample acceptance unit are in different locations), locked transport bags must also be used. In the external laboratory transfer (the sampling unit and the laboratory sample acceptance unit are in different institutions), the sample should be placed in two plastic bags inside of each other to prevent leakage. The carrying bags should be resistant to external impacts and environmental conditions and it should be with a cooler.

Analysis in authorized and audited laboratories: Drug abuse testing should be performed in licensed medical laboratories that meet quality and safety requirements by the Ministry of Health in Turkey.

In the drug abuse testing process, the fulfillment of certain quality and safety requirements can be handled within the framework of the quality management system. For laboratories, this is a costly and voluntary process. Also, it cannot replace of licensing from the Minister of Health. But it is facilitates the requirements to obtain the license.

For this purpose, the internationally ISO 15189 accreditation (Standard for Medical Laboratories Quality and Competence) is ideal for medical laboratories. Accreditation of ISO 9001 (Requirements for Quality Management Systems) or ISO 17025 (Standard of General Requirements for Qualification of Testing and Calibration Laboratories) accreditation is also useful for establishing quality management system (ISO 15189:2007: Medical laboratories – particular requirements for quality and competence 2007, ISO 17025:2005: General requirements for the competence of testing and calibration laboratories 2005).

Specimen validity tests: Have been applied to find the manipulations that drug users use to prevent the determination of drug use. If urine integrity is lost, urine is rejected for drug abuse testing.

After the sample is delivered, the urine composition (such as creatinine, pH, density, nitrite, and oxidant) should be analyzed for suitability (Cook et al. 2000). Sample acceptance and rejection criteria for cheating should be determined. If the sample is deemed fraudulent, the statement "diluted, integrity is impaired or sample is not urine," should be stated in the drug test report. Some of the sample control and integrity tests from the criteria may not always require sample rejection. It is appropriate to evaluate sample integrity tests together (Phan et al. 2012).

The reliable testing methods: Today drug screening tests are applied by immunochemical analysis methods, while the drug confirmation tests are done by chromatographic methods. Three analytical methods for drug screening purposes can be used: (1) Point of care tests: It is based on immunochemical method (immunochromatography) (Melanson 2009). It is suitable for medical use in clinics (can be used in emergency unit and intensive care unit). In Turkey, the Ministry of Health has said that the point of care test results for forensic or administrative purposes should not be used, because of their varying analytical performances, inability to implement quality control in real sense, problems in the evaluation of results, and different threshold concentrations in today's technology. (2) Immunochemical laboratory tests: It is based on immunochemical methods such as enzyme multiplied immunoassay technique (EMIT), cloned enzyme donor immunoassay (CEDIA), fluorescence polarization immunoassay (FPIA) or kinetic interaction of microparticles in solution

(KIMS). These methods with the high sensitivity, the small sample volume requirement, and the quick results in automatized devices offer advantages. The performance of the test depends on the properties of the antibody. This leads to cross-reactivity and false positivity to similar drugs (low specificity) (Melanson 2012). (3) Chromatographical laboratory tests: Gas Chromatography – Mass Spectrometry (GC-MS) versus Liquid Chromatography – Tandem Mass Spectrometry (LC-MS/MS). Applications are not yet widely used for screening purposes due to device investment costs, application difficulties, and reasons for not being practical. This methods may be preferred since they are at lower rates for false positive and negative results (Zhang et al. 2016).

Cross-reactivity is defined as the analytical method that does not distinguish between tested drugs and chemically similar drugs. It is a very important issue in evaluating the test results. The measurement of similar structure of substances and metabolites in drug groups are provided by immunochemical methods. This measurement is due to the cross-reactivity of the antibody used to the specific drug variants. The performance of the analytical method used to measure some substances in the group to which it belongs may not be measurable. However, cross-reacting antibodies to molecules outside the drug is a problem that causes false positives. For this reason, potential cross-reactivity specific to the method of measurement should be known and should be asked, if any, for the drug or herbal product the patient is using to determine the cause (Smith and Bluth 2016).

The strict quality control and and assurance: For the test results to be used as evidence, it must be carefully analyzed. Standardized and validated procedures spesific for the sample must be used. The methods should be verified and validated in laboratory before any analysis of patient sample.

The quality control requirements are determined according to the drug abuse testing purpose. At least two levels of daily internal quality control samples are required prior to analysis (TDM8-A: Urine drug testing in the clinical laboratory Approved guideline 1999). The blind sample (the identity stored from the workstation) can be monitored for the quality of the laboratory phases by barcoding and analyzing like a patient sample. In addition, drug abuse testing should be monitored by an external quality control program.

Two-step analysis: Drug abuse testing is applied step by step in the form of screening and confirmation testing. The screening tests are applied first and the results are reported. After the results are assessed, second-step confirmatory tests are then applied in the case of objection in terms of false negativity or positivity. The confirmation test results are reported. The screening tests are based on immunochemical methods. They are qualitative or semiquantitative and detect the presence of the drug and/or its metabolites (Melanson 2012). The confirmation tests are based on chromatographic methods (GC-MS or LC-MSMS). They are quantitative and confirm drug presence or measure the concentration of the drug (Yuan et al. 2015).

In terms of drug abuse testing, the screening and confirmation testing should be considered as an integral part of each other. The two systems should work together to provide strong protection against accusations of drug use. The screening tests are fast and cheap, but also have to be a quality (sensitive to high) that positively excludes all negatives correctly. The confirmation tests are slow and expensive, but should identify positive or negative screening tests (specificity high). These properties depend on the technology used as the method of analysis. In today's technology, only one or two target analytes are detected clearly in the confirmation tests while all the target analytes are roughly determined in the screening tests.

The storage of the split specimen: A split sample is a specimen taken for screening and collected with observation, delivered to the laboratory in accordance with the rules of the security chain and stored under appropriate conditions for re-analysis if necessary by confirmation methods. For urine samples, samples taken from different containers or separated from the same container can be used. To prevent individual victimization, particularly positive samples should be stored.If necessary, confirmated in terms of false positives. If appropriate, negative samples may be stored in some centers for false negativity and person identification from residue nucleic acids in the specimen.

The confirmation of the split specimen in case of objection: Negative drug sccreening test results usually do not require confirmation tests. However, if incompatible clinical results are obtained communication with the physician and laboratory should be done. Possible situations should be questioned. If necessary, new samples should be taken and replicates analyzed or confirmation analysis requested. Because negative samples are stored in the laboratory until the result of the test is evaluated by the physician, the clinical and laboratory communication should be fast so that confirmation can be done. The positive screening test result is sent to confirmation analysis when necessary. The split samples of positive samples are stored for a long period of time and are referred to the confirmation analysis if applied within this time.

There are two approaches in practice for samples that are positive for the screening result: (1) Confirmation of each positive sample: In this case, every sample that is positive without the need of a re-test request is sent to the drug confirmation laboratory. However, this approach has limitations in implementation due to unnecessary workload, delayed turnaround time, and cost. There is also the case where patients agree with physician or when the test results may not always be used as a judge in a judicial or administrative decision. (2) Confirmation

of objection to positive sample: In this case, if the patient is found to be incompatible with his clinical examination by the physician or if he claims to be a victim, a confirmation test is requested by the judicial authorities or physcian. This approach has been reported to save 95% cost (Lum 2002). However regardless of the approach, the opportunity for confirmation of positive results should be provided. Against negative medical, judicial, financial, or social consequences, the right to health, liberty, humanitarian life, or equality of individuals is regulated by the Constitution and by international regulations at the national level (The European Convention on Human Rights 1954, Constitution of the Republic of Turkey 1982). For this reason, the state should prevent individuals from becoming victims by making legal / administrative regulations and audit the applications.

The result custody chain: The result custody chain should be managed to provide continuous information accessibility, confidentiality, and recoverability. The information required for the given laboratory service should be accessible. Authorities and responsibilities in the information system should be defined (information access, information entry, information exchange, and information dissemination), personal passwords should not be shared, and hardware and software measures should be taken in the information system. Information system safeguards should be taken againist authorized persons changing the results againist unauthorized outside entry into the system. In addition, the results of drug abuse testing should not be given either verbally or in writing. Only the requesting physician or institution should have open access to the result. A limited number of people must be authorized to change the outcome.

The appropriate cut-off concentration: It is the drug concentration from which the negative or positive decision is made. Since it affects false negativity and false positivity, it is the most critical issue in terms of drug abuse testing. Depending on the intended use, different cut-off concentrations can be used. Therefore, the physicians should pay attention to the cut-off concentration in the test report.

The cut-off concentrations are determined in three ways: (1) Analitical cut-off concentrations: The level at which the parent molecule or metabolite of a drug can be determined by the method of analysis (level of analytical sensitivity). (2) Diagnostic cut-off concentrations: The optimal sensitivity and specificity are determined with tools like Receiver Operating Characteristic (ROC) curves. The cut-off concentrations are determined at high sensitivity (lowest value for false negatives) for screening tests and at high specificity (lowest value for false positives) for confirmation tests. (3) Administrative cut-off concentrations: The level is low level enough to keep the number of false positives caused by exposure to the drug (such as nutrition and passive use) to a minimum. In addition, it is important to determine the drug use within a reasonable period of time, which is usually well above the level that can be determined by the method of analysis of the substance. Administrative cut-off concentrations are generally not suitable for medical purposes. These cut-off concentrations can lead to false negative test results, and result in problems in terms of diagnosis and treatment.

The analytical or diagnostic cut-off concentrations are recommended for medical drug abuse testing, whereas administrative cut-off concentrations are recommended for forensic and administrative purposes. Administrative cut-off concentrations are a legal requirement in state legislation or a recommendation in the guidelines of professional associations (Clinical Drug Testing in Primary Care 2012). In practice, medical laboratories may use more than one cut-off concentration for the same test (such as screening or confirmation tests) for different purposes of request (for medical, judicial, or administrative purposes). However, the performance of the test method should be validated for each selected cut-off concentration.

While the administrative cut-off concentration in Turkey is determined for the alcohol level by the Traffic Law, it has not yet been determined for drug abuse testing (Road Traffic Law 1983). In daily practice, drug abuse test results obtained from different laboratories in Turkey are evaluated with different cut-off concentrations. Legislative changes may also provide national standardization (The Principles of Operation of Medical Laboratories and the Medical Laboratories at the Substance Abuse Diagnosis and Treatment Centers that Makes Illegal and Abused Drug and Substance Analysis in Urine Samples 2016).

The appropriate interpretation of the results: When interpreting the test result, one should consider the limitations of the measurement method used, the determination of which drugs and metabolites are not identified, the possible cross-reacting compounds, the limitations of the selected sample type, and the purpose of the test.

The interpretation of negative or positive test result should be as follows: (1) Interpretation of negative test results: The negative test result is one that falls below the cut-off concentration. A negative result can be true or false. A true negative is a drug not actually present in the sample and is not detected by analytical method (no drug and test negative), which is the desired result. False negativity is a drug present in the sample but cannot be determined analytically (drug present and test negative). This may result from possible situations such as low concentration of the drug, low frequency of drug intake, cheating on the urine sample, not searching for the right drug, insufficient sensitivity of the method, or sampling at a time other than the detection window.

Two important problems causing negativity are detection window and fraud. Safety procedures can not completely

prevent manipulation. Clinical correlation and sample integrity tests are the only tools that can be used to detect cheating. Because the detection window is influenced by many factors, it can cause a negative result depending on individual variability. Repeated and/or alternative sampling of samples may be used to detect chronic use.

Synthetic cannabinoids (street name 'Bonzai') commonly used in Turkey in recent years are among the new generation of drugs that cause false negatives in screening tests (Synthetic Cannabinoids 2016). These materials, which can only be identified by confirmation tests, make it difficult to fight the war in the international arena.

(2) Interpretation of positive test results: The positive test result is a result that is above the cut-off concentration. A positive test result may be true or false: True positivity is a drug present in the sample with detectability by an analytical method (drug present and test positive). False positivity is a drug that is not actually present in the sample but detected by an analytical method (no drug and test positive). This can be caused by possible situations such as past drug use history (chronic users), passive inhalation (cannabis, cocaine), cross-reactions (prescription or non-prescription drug, herbal product, food use), and/or interactors (structurally similar or with dissimilar drugs) (Makkai 2000).

The positive screening test result does not define the sample person as the definite drug user. In evaluating the results, the individual needs an alternative medical evaluation with detailed information. In addition, a possible decision regarding the physical condition, mental state, or behavior at the time of the event (or the presence of a custody) supports the drug use. If the analysis is performed by immunochemical methods, the physician should ask the laboratory for the major cross-reactive compounds expected for each test group.

RESULTS

According to last regulations in Turkey, physicians have to know and apply the quality and safety requirements of drug abuse testing. Relevant regulations and technical issues should be well understood in this framework. Drug abuse testing applied in the clinics should not victimize the patient or the worker unnecessarily and should function in accordance with the scientific principles required.

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