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The following pages provide supplemental technical information and explanations as a companion to the *AT Forum* special white-paper research report *SAM in MMT** (*Substance-Abuse Monitoring in Methadone Maintenance Treatment).

Terms Defining Drug Screen/Test Performance

Understanding Cutoff Values of Drug Screens

Cutoff Levels, Detection Times, X-Reactivity

How Typical On-Site Drug Screening Devices Work


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SAM in MMT*

*Substance-Abuse Monitoring in Methadone Maintenance Treatment

Stewart B. Leavitt, PhD, Editor, AT Forum and the SAM Review Panel**

The Vital Necessity of SAM

Early-Warning System

The complete *SAM in MMT* white-paper report may be downloaded at no charge from the ATForum.com website – http://www.atforum.com – listed under the "Addiction Resources" tab.

The specific URL is:
http://www.atforum.com/SiteRoot/pages/addiction_resources/SAMinMMT-FINALApril2005.pdf

See the *SAM in MMT* paper for complete citations regarding references listed on the following pages.

Addiction Treatment Forum
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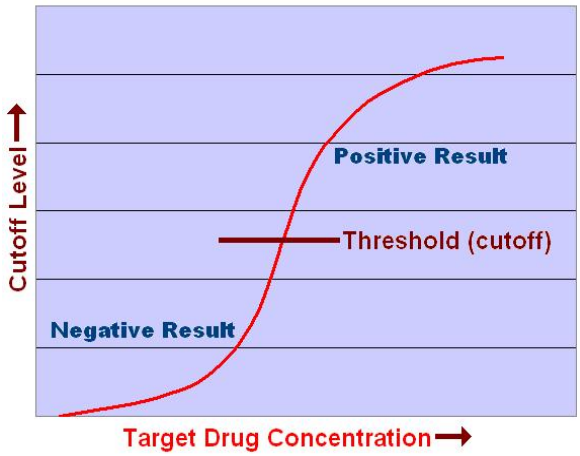
Terms Defining Drug Screen/Test Performance

Screen	A relatively uncomplicated, noninstrumented, rapid, and cost-effective assay. Effective screens have high predictive value (see below) for ruling out the presence of a target substance or drug class in a specimen; however, the specificity of screening assays is often less than adequate to confirm positive results.
Test	A more complex and elaborate instrumented assay for specimen analysis, which usually has both high sensitivity and high specificity. Good quality, properly performed tests are reliable and accurate for *confirming* the presence of targeted substances.
True Negative (TN)	The target substance is entirely absent from the specimen or below the assay cutoff point.
True Positive (TP)	The target substance is present in the specimen at a concentration equal to or greater than the cutoff point of the assay.
False Negative (FN)	A target substance or drug class is indicated as being absent when, in fact, it is present in the specimen. The false result may be due to inaccuracies in procedure or specimen tampering — adulteration, dilution, substitution — or there is less drug than can be detected.
False Positive (FP)	The assay indicates a target substance or drug class is present when it is not. This may be due to procedure inaccuracy or the presence of another substance that the screen or test mistakes for the target drug, called, cross-reactivity (see below).
Sensitivity	The ability of the assay to detect the target substance or drug class when it is present. An assay with high sensitivity would be comprehensive in detecting the presence of the target substance or drug class, and would produce relatively few false-negative results. **Formula for calculating Sensitivity = TP ÷ (TP+FN)**
Sensitivity Limit	Often called "detection limit" = least amount of substance in the specimen that the assay can detect.
Cutoff Point	Concentration established as a breakpoint or threshold for labeling a result as either positive or negative.
Specificity	Generally described as the ability to distinguish different substances or classes; e.g., identify whether an opioid is morphine, codeine, or poppy seeds. It is the ability of the assay to selectively produce a negative result when the particular substance or drug class of interest is truly absent. An assay with high specificity would produce few false-positive results. **Specificity = TN ÷ (TN+FP)**
Accuracy	An overall measure of how consistently well an assay performs. This is the proportion of true results (positive or negative) that the assay is capable of producing across a number of different samples. Sometimes called "efficiency" or "agreement." **Accuracy = (TP+TN) ÷ *n* (*number of samples evaluated*)**
Reliability	Also called "reproducibility" or "precision," This is a measure of whether the assay will consistently produce (replicate) the same results on specimens with target substance at the same concentration. Low reliability would suggest that from one time to the next different results might be obtained and the assay cannot be trusted.
Negative Predictive Value (NPV)	NPV is the probability that a negative result indicates that the targeted substance or drug class is *truly not present*. Good quality assays have high NPV for reliably *ruling-out* the presence of targeted substances. It answers the question: Can negative results with this assay be trusted? **NPV = TN ÷ (FN+TN)**
Positive Predictive Value (PPV)	PPV is the probability that a positive result indicates that the targeted substance or drug class is *actually present*. Good-quality assays have high PPV for confirming (*ruling-in*) the presence of a substance or drug class. It answers the question: Can positive results with this assay be trusted? **PPV = TP ÷ (FP+TP)**
Cross-Reactivity	Substances with chemical structures similar to the targeted substance may produce false-positive results when immunoassays with less specificity are used. This is less of a problem with chromatographic assays employed for confirmatory testing. It cannot always be assumed that drugs with similar function will cross-react: e.g., the opioid analgesics propoxyphene and meperidine do not cross-react in the opiate assay due to their very different chemical structures.

Sources: Cone 1997; Grönholm and Lillsunde 2001; Hawks 1986; Marion 1993; SAMHSA/CSAP 1999; Wu 2002.

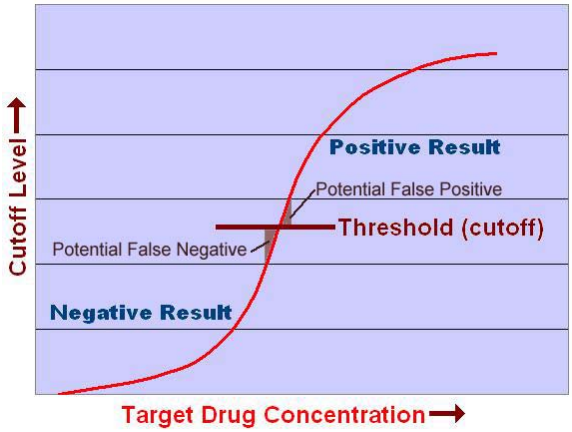
Understanding Cutoff Values of Drug Screens

Drug screens are qualitative only, providing “yes” or “no” answers, and cannot tell *how much* of a substance is in a specimen. The detection curve for a targeted drug is S-shaped: that is, it flattens out at lower and higher concentrations and the curve changes most rapidly around the cutoff point (***graph*** at right).



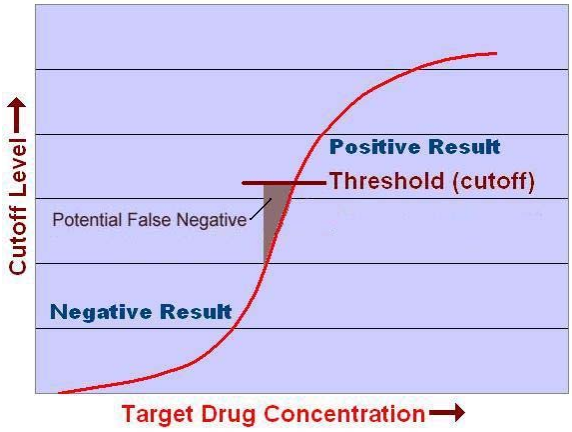
Since the cutoff point is used as a breakpoint or threshold for labeling a result as either positive or negative, it can be imagined that it would be more accurate if drug concentration was more stable at this level. However, this is not the case.

Consequently, screens are less accurate for drug concentrations that are close to the cutoff point. There is a potential here for false positive or false negative results (middle ***graph*** at right).



The accuracy of a screen is greatest when target substance concentrations are more than 25% below or more than 25% above the cutoff value (i.e., <75% or >125%). Fortunately, drug concentrations of MMT patients are almost always in those ranges, so screens provide adequately accurate results for most clinical purposes and confirmatory testing is commonly needed only in special circumstances.

A higher cutoff level increases assay specificity; that is, it will produce few if any false positives. But it also increases the chances of “missing” drug that is actually present and may indicate false negative results (***graph*** at right). Cutoff levels for screens are often higher than for tests, since tests (e.g., GC/MS) are expected to be capable of accurately detecting much smaller quantities of drug present at lower cutoff levels.



In sum, the cutoff levels of screens are typically set high enough to produce as few *false positives* as possible but, at the same time, to limit the potential for *false negatives*. In this way, screens can usually be trusted to “rule-out” the presence of target substances; however, in some cases positive results may need confirmation via testing procedures that are more specific (and, therefore, can be trusted to “rule-in” the drug of interest).

Cutoff Levels, Detection Times, X-Reactivity

Target Substance (analyte) or Drug Class Screened/Tested	Positive Initial Screen Cutoff ng/mL Urine *(Oral Fluid)*	Positive Confirmatory Test Cutoff ng/mL Urine *(Oral Fluid)*	Duration of Detectability Urine* *(Oral Fluid)***	Some Cross-Reactive Substances That May Cause Preliminary Misleading or False Positive Results***
Amphetamines (AMP)	1,000 [1] **500** [2] *(50)* [2]			amantadine, bupropion, chloroquine, chlorpromazine, desipramine, dextroamphetamine, ephedrine, fenfluramine, labetalol, mexiletine, n-acetyl procainamide, phentermine, phenylephrine, phenylpropanolamine, propanolol, pseudoephedrine, quinacrine, ranitidine, selegiline, trazodone, tyramine
Amphetamine		500 [1] **250** [2] *(50)* [2]	2-4 days *(20-50 hr)*	
Methamphetamine (MET)		500 [1] **250** [2] *(50)* [2]	2 days *(>24 hr)*	
MDMA (Ecstasy, XTC)	**500** [1,2] *(50)* [2]	**250** [1,2] *(50)* [2]	1.5-2 days	
Barbiturates (BAR) ▪ short-acting ▪ intermediate ▪ long-acting	**300** [3]	**200** [3]	1 day 2-3 days 7+ days (up to 30)	phenytoin
Benzodiazepines (BZD) ▪ ultra-short-acting[a] ▪ short-acting[b] ▪ Intermediate[c] ▪ long-acting[d]	**300** [3]	**200** [3]	12 hours 1 day ~2-3 days 7+ days (up to 30)	oxaprozin, sertraline
Cannabinoids (THC) (marijuana metabolite) ▪ light smoker ▪ moderate (4x/wk) ▪ heavy use (daily) ▪ chronic heavy use	**50** [1,2] *(4)* [2]	**15** [1,2] *(2)* [2]	*(4-10 hr)* Up to 3 days 4-5 days 10 days 20-28 days (up to 36)	dronabinol, efavirenz, hemp seed oil
Cocaine (COC) (parent drug)			6-8 hours *(4-12 hr)*	topical anesthetics containing cocaine (e.g., TAC solution)
Cocaine metabolites (benzoylecgonine)	300 [1] **150** [2] *(20)* [2]	150 [1] **100** [2] *(8)* [2]	2-4 days; up to 8 days in heavy use *(12-24 hr)*	
Methadone (MTD) during MMT	**300** [3,4]	**300** [3,4]	7-9 days *(>24 hr)*	
Opiates (OPI) (excluding methadone)	**2,000** [1,2] *(40)* [2]		1-3 days	fluoroquinolones, ofloxacin, papaverine, poppy seeds, rifampicin/rifampin
6-acetylmorphine (MAM) *(metabolite of heroin)*		**10** [1,2] *(4)* [2]	2-4 hours *(1-4 hr)*	
Morphine/heroin[e] (MOR)		**2,000** [1,2,4] *(40)* [2]	2-3 days *(12-24 hr)*	
Codeine (COD)		**2,000** [1,2,4] *(40)* [2]	2-3 days *(24-36 hr)*	
Phencyclidine (PCP) ▪ Chronic use	**25** [1,2] *(10)* [2]	**25** [1,2] *(10)* [2]	7-14 days Up to 30 days (avg. 14)	dextromethorphan, diphenhydramine, thioridazine

Data assimilated from: Cone 1997; Cone and Preston 1999; Federal Register 2004; Gourlay et al. 2004; Heit and Gourlay 2004; Med Letter 2002; STL 2004; Samyn et al. 1999; Schuckit 2000; Simpson et al. 1997; Strang 1999; Warner 2003; Wolff et al. 1999.

[a] half-life 2 hours (e.g., midazolam); [b] half-life 2-6 hours (e.g., triazolam); [c] half-life 6-24 hours (e.g., temazepam/chlordiazepoxide); [d] half-life 24 hours (e.g., diazepam/nitrazepam); [e] heroin is usually detected as its longer-lasting morphine metabolite.

[1] Cutoffs in DHHS guidelines for Federal Workplace Drug Testing Programs (urine); last revised November 13, 1998 (63 FR 63483).

[2] Cutoffs as proposed by DHHS for **urine** and oral fluid; Federal Register, 2004 (April 13);69(71):19644-19732. APPROVAL PENDING.

[3] Sources: Cone 1997; Cone and Preston 1999. *Note:* Thresholds may vary by laboratory and/or the assay used.

[4] The threshold for some methadone screens is 150 ng/mL, with confirmatory testing cutoffs for methadone and EDDP at 120 ng/mL or less. Confirmatory clinical testing for morphine and codeine in urine is more typically at 300 ng/mL

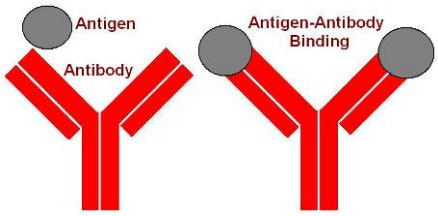
* *General guidelines only* – Interpretation of retention times must take into account cutoff values for assay and variability of testing specimens, drug metabolism and half-life, patient physical condition, fluid intake, and route, frequency, and duration of drug administration.

** Detection times noted in oral fluid are via GC-MS, after limited drug dosing, at cutoff levels lower than DHHS guidelines (Samyn et al. 1999).

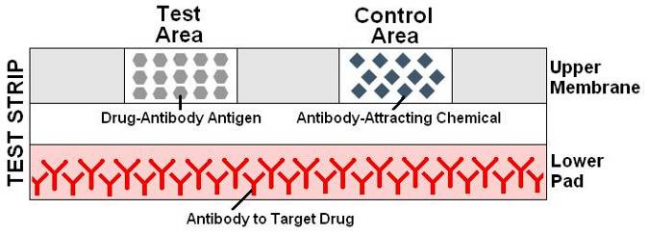
*** Sources: Med Letter 2002; Warner 2003. Products containing the generic compounds listed are marketed under a variety of brand names. Not all screens or tests share the same cross-reactivity and it is best to check with the particular assay manufacturer.

How Typical On-Site Drug Screening Devices Work

On-site point-of-care (POC) screening devices are typically qualitative, competitive immunoassays using a lateral-flow chromatographic process to rapidly show results in color. Scientifically, they work by using antigen-to-antibody binding that is characteristic of immune-system function in the body. That is, antibodies attach to and bind antigens (such as, foreign chemicals or substances) so they can be neutralized and eliminated from the body.

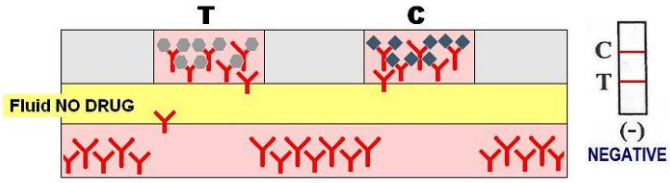


Essentially, a screen-device test strip is a sandwich of two layers containing antibody in the bottom layer and a special chemical antigen in the top layer.

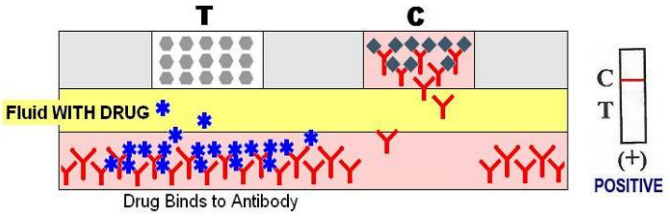


- The bottom layer (pad) has color-saturated antibodies that can stick to (bind) a targeted substance of abuse or its metabolite, which acts as an antigen if it is present.
- The top layer (membrane) has special antigens in a "Test Area." These will attract the colored antibodies from the bottom layer if nothing interferes (competes) with their binding, such as drug in the specimen fluid. There also is a "Control Area" coated with a special chemical that will attract and bind to colored antibody.
- As specimen fluid flows (migrates) through the strip (*via lateral flow capillary action*), colored antibodies in the bottom layer are released to bind with either the target substance, if it is present, or with antigen in the Test Area.

- If the target substance is *not present* (or present in a very low amount below the detection level), the colored antibody will be free to attach to antigen molecules on the Test (T) Area to produce a visible colored T line — indicating that the screen is *negative*.



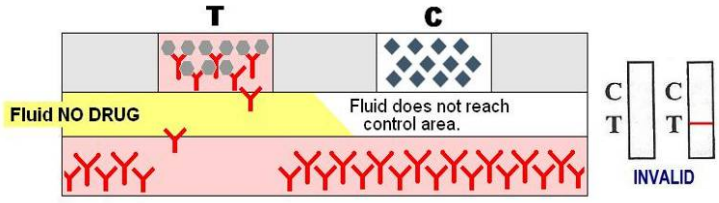
- If a sufficient quantity of the target substance is *present*, it will grab (bind to) the colored antibodies and prevent them from reaching the Test Area of the strip — thus, *no* colored line shows up in the Test (T) Area and this indicates the result for the target substance is *positive*.



***Note**: This is somewhat counterintuitive, in that one might expect a positive test to be indicated by the presence of a color, rather than its absence as is the case with these devices.*

On-site screening devices also have a colored line appearing in the "Control Area" as a form of quality assurance to indicate the screen is valid.

- This Control (C) Area, in the top layer of the test strip, has special immunochemical proteins that attract and bind to the colored antibodies from the lower layer, whether or not the target drug is present.
- Presence of the colored C line (see examples above) indicates sufficient specimen fluid was added to assure proper flow (wicking or capillary action) on the test strip and that the colored antibodies and other chemicals are still viable and active. However, the ***absence*** of a colored line in the Control (C) Area invalidates the assay, whether or not a line appears in the Test (T) Area.



- An invalid assay *does not* indicate that the specimen itself was substituted, adulterated, diluted or is otherwise unsuitable.