ARUP® LABORATORIES | NATIONAL REFERENCE LABORATORY

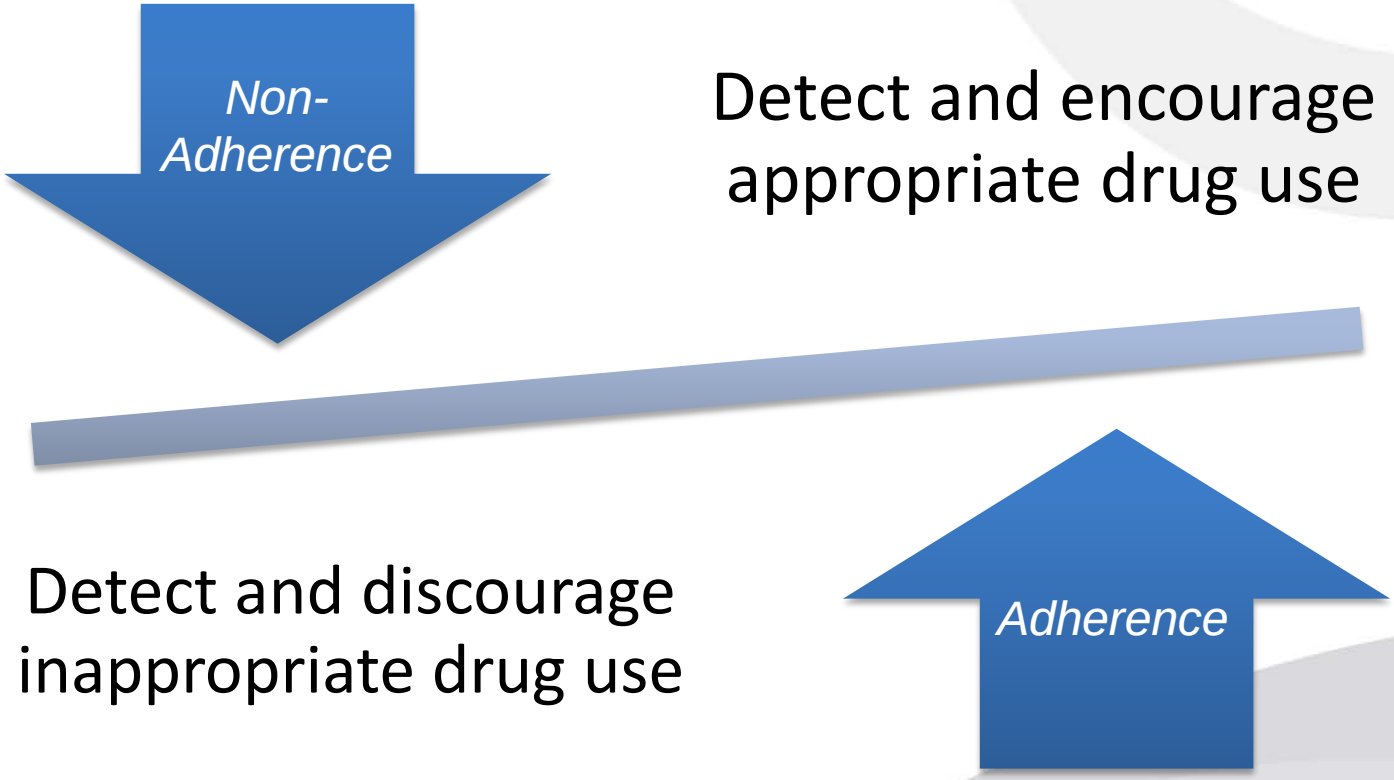
Appropriate utilization of drug tests for pain management patients

Gwen McMillin, PhD, DABCC (CC, TC)
Medical Director, Toxicology, ARUP Laboratories
Associate Professor (clinical), University of Utah

Drug testing in pain management

- Baseline testing
- Routine testing
  - Periodic, based on patient risk assessment
  - To evaluate changes
    - Therapeutic plan (drugs, formulations, dosing)
    - Clinical response (poor pain control, toxicity)
    - Clinical events (disease, surgery, pregnancy)
    - Patient behavior

Objectives of drug testing

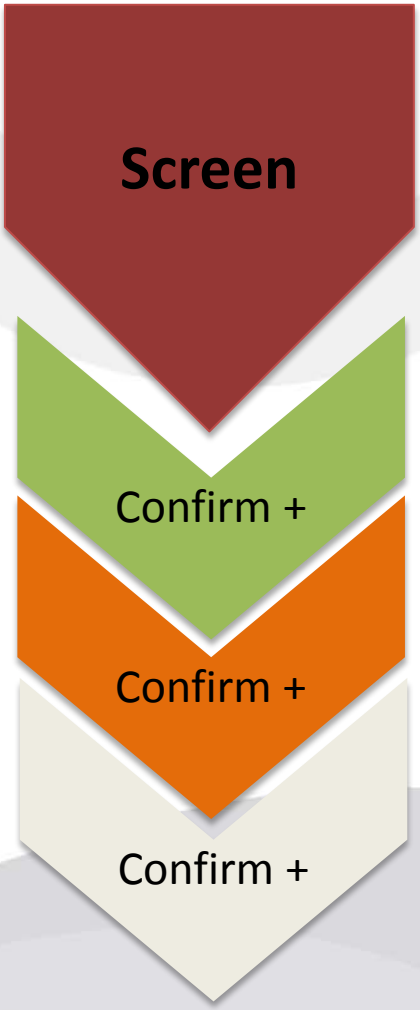


Traditional approach

- Immunoassay-based screen
- Confirm positive results with a mass spectrometric method (GC-MS, LC-MS)

Not appropriate for pain management

- Need to confirm positive screen results is limited to certain drug classes
- Confirmation of negative screen results may be important
- Immunoassays are not useful for detection of all drugs of interest



Positivity rates in urine drug testing for pain management

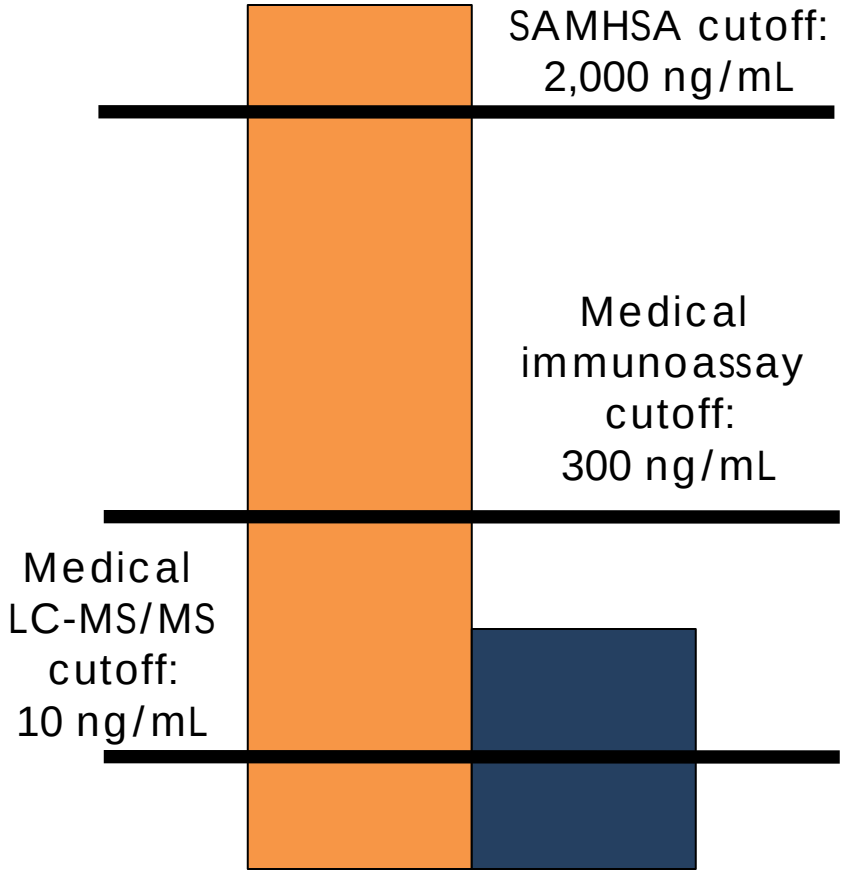
- ~80% of urine specimens collected for the purpose of adherence testing are positive
- <5% of positive results fail to confirm, with the exception of amphetamine tests
- False negative results occur frequently

Positive results "missed" by immunoassay vs LC-MS/MS

Compound	Immunoassay cutoff (ng/mL)	LC-MS/MS cutoff (ng/mL)	% missed by immunoassay (total n ~8000)
Codeine	300	50	29.6% (45)
Hydrocodone		50	23.3% (701)
Hydromorphone		50	69.3% (1878)
Alprazolam	200	20	53.3% (646)
Nordiazepam		40	40.0% (320)
Clonazepam		40	66.1% (119)

Mikel et al., *TDM* 31(6):746-8, 2009
West et al., *Pain Physician* 13:71-8, 2010

Immunoassay detection



- Cutoff
- Calibrator
- Cross-reactivity profile of the immunoassay

Concentrations (ng/mL) required to trigger a positive opiate (300 ng/mL cutoff)

	EMIT	CEDIA	Triage
Morphine	300	300	300
Codeine	247	300	300
6-monoacetylmorphine	1088	300	400
Hydrocodone	364	300	300
Hydromorphone	498	300	500
Oxycodone	5,388	10,000	20,000
Oxymorphone	>20,000	20,000	40,000
Noroxymorphone	-	-	-

False negatives likely

Concentrations (ng/mL) required to trigger a benzodiazepine positive (300 ng/mL cutoff)

	EMIT	Nex Screen	Triage
Alprazolam	79	400	100
Alpha-OH-alprazolam	150	N/A	100
Clonazepam	500	5,000	650
7-amino-clonazepam	11,000	N/A	N/A
Chlordiazepoxide	7,800	8,000	13,000
Nordiazepam	140	500	700
Diazepam	120	2,000	200
Oxazepam	350	300	3,500
Temazepam	210	200	200
Lorazepam	890	4,000	200

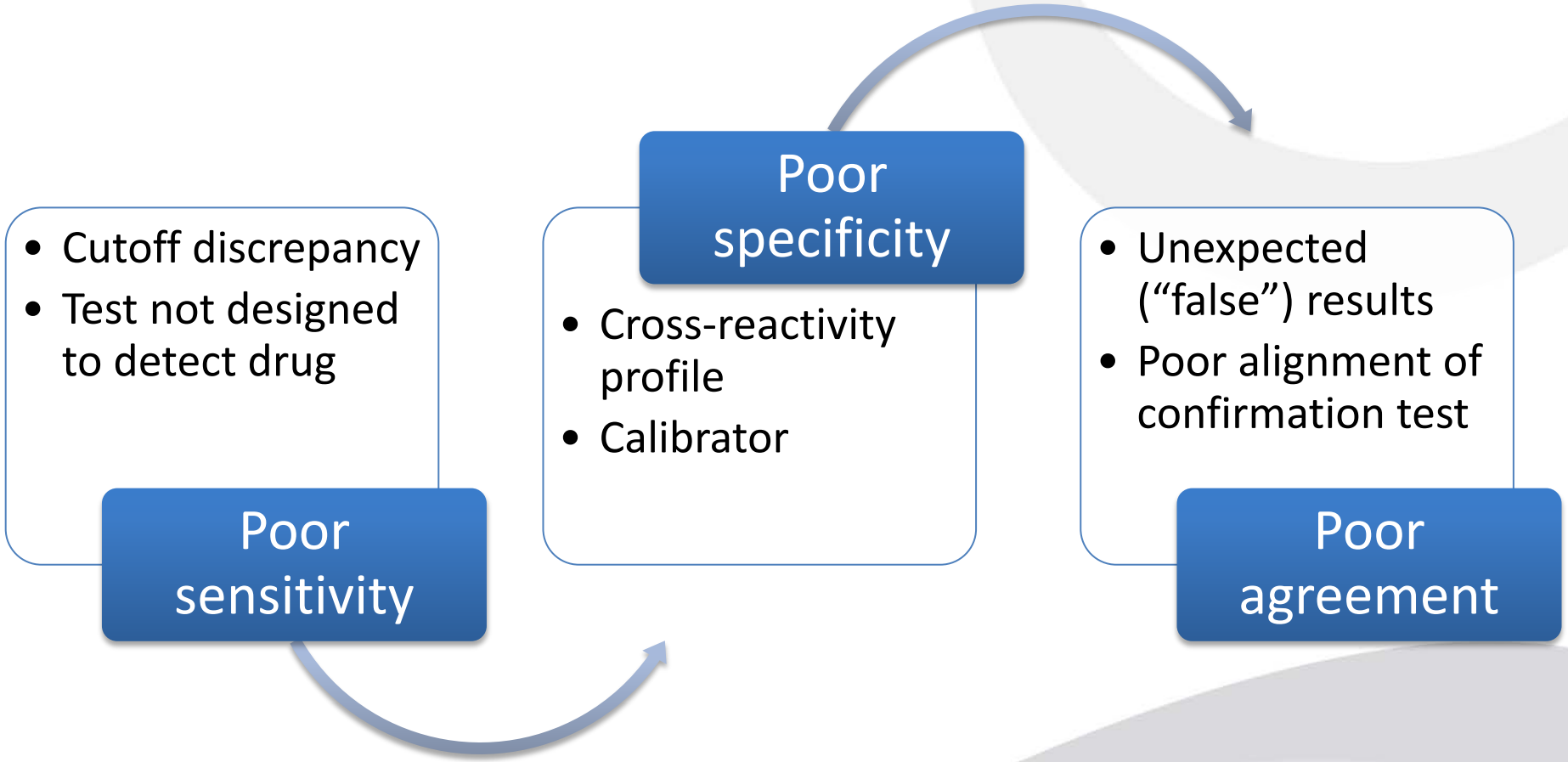
False negatives likely

Drugs that could cause a false positive amphetamine test

- N-acetylprocainamide
- Chlorpromazine
- Phenylpropanolamine
- Brompheniramine
- Trimethobenzamide
- Pseudoephedrine
- Tolmentin
- Propylhexedrine
- Ranitidine
- Labetalol
- Perazine
- Promethazine
- Quinicrine
- Buflomedil
- Fenfluramine
- Mephentermine
- Phenmetrazine
- Tyramine
- Ephedrine
- Talmetin
- Nylidrin
- Isoxsuprine
- Chloroquine
- Isometheptene
- Mexiletine
- Phentermine
- Ritodrine

Adapted from: Broussard L, Handbook of Drug Monitoring Methods, Humana Press, 2007

Performance challenges

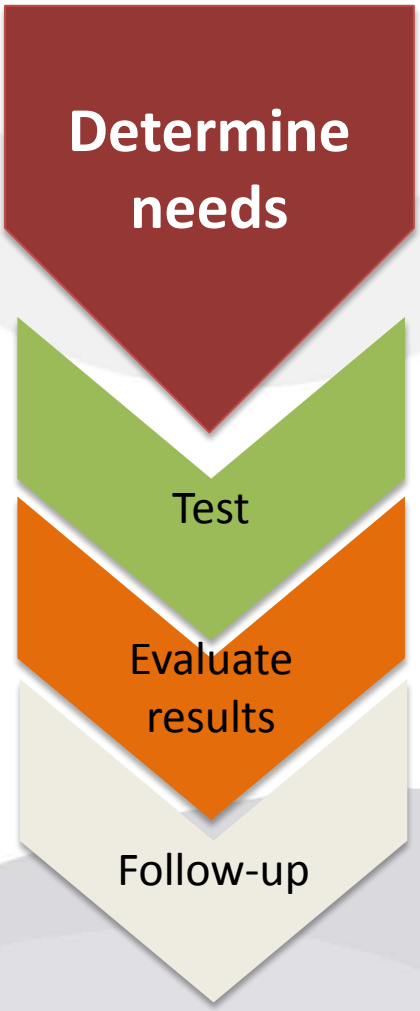


Impact of traditional approach

- Inappropriate selection and interpretation of screen results
- Inappropriate selection and interpretation of confirmation tests
- Unnecessary costs of testing associated with inappropriate testing
- Poor patient-provider-laboratory relationships

Evolving approach

- Understand needs
- Understand testing options and limitations
- Select best test
- Evaluate results
- Targeted testing for unexpected or inadequate results, or when quantitation is needed



Case Example 1

- Pharmacy history
  - Prescribed methadone and lisdexamfetamine dimesylate
- Screen results
  - **POSITIVE** for methadone, amphetamine, and THC
  - **NEGATIVE** for methamphetamine, oxycodone, opiates, and all other drug classes tested
- Patient history
  - Admits to occasional use of marijuana (THC)

Case Example 1 (cont)

- Interpretation based on expectations:

  Results are consistent with expectations

  – Confirmation tests not needed

  – Document results of investigation and final interpretation

- Reflex testing approach:

  – 3 confirmation tests would have been ordered

  – Additional office visit(s) may have been required

Unnecessary expenses!!!

Case Example 2

- Pharmacy history
  - Prescribed oxycodone, hydrocodone, clonazepam, and methylphenidate
- Screen results
  - **POSITIVE** for oxycodone and opiates
  - **NEGATIVE** for benzodiazepines, amphetamines, and all other drug classes tested
- Patient history
  - Insists on adherence to prescribed therapy

Case Example 2 (cont)

- Interpretation based on expectations:

  results are NOT consistent with expectations

- Post-analytical investigation (laboratory):
  - Clonazepam sensitivity of the benzodiazepine screening test that was used is poor
  - Methylphenidate is not detected by the screen

Case Example 2 (cont)

- Interpretation based on expectations:

  results are consistent with expectations

- Post-analytical investigation (laboratory):
  - Clonazepam sensitivity of the benzodiazepine screening test that was used is poor
  - Methylphenidate is not detected by the screen

Case Example 2 (cont)

Recommendation:

- Confirm periodically, if concern arises, and/or if results impact clinical management decisions
- Document results of investigation and final interpretation

- **Reflex testing approach:**
  - 1 confirmation test would have been ordered
  - 2 possible false negative results remain unresolved
  - Could compromise patient care and relationship between the physician and the laboratory

Is adulteration testing necessary?

Adulteration in urine drug testing

- Reduce signal/noise
  - Dilute specimen
  - Increase analytical noise
- Prevent drug-antibody interactions
  - Charge interactions (pH)
- Destroy drug analytes
- **Mimic drug use**
  - **Urine substitution**
  - **Direct addition of drug to urine**

Examples of urine substitutes

- Beverages
- Animal urine
- Synthetic urine
- Human urine
  - Purchased
  - Obtained from friend or relative
  - Archived by patient

Common forms of adulteration testing

- Temperature
- Visual inspection
- Creatinine
- Specific gravity
- Nitrates
- Oxidants

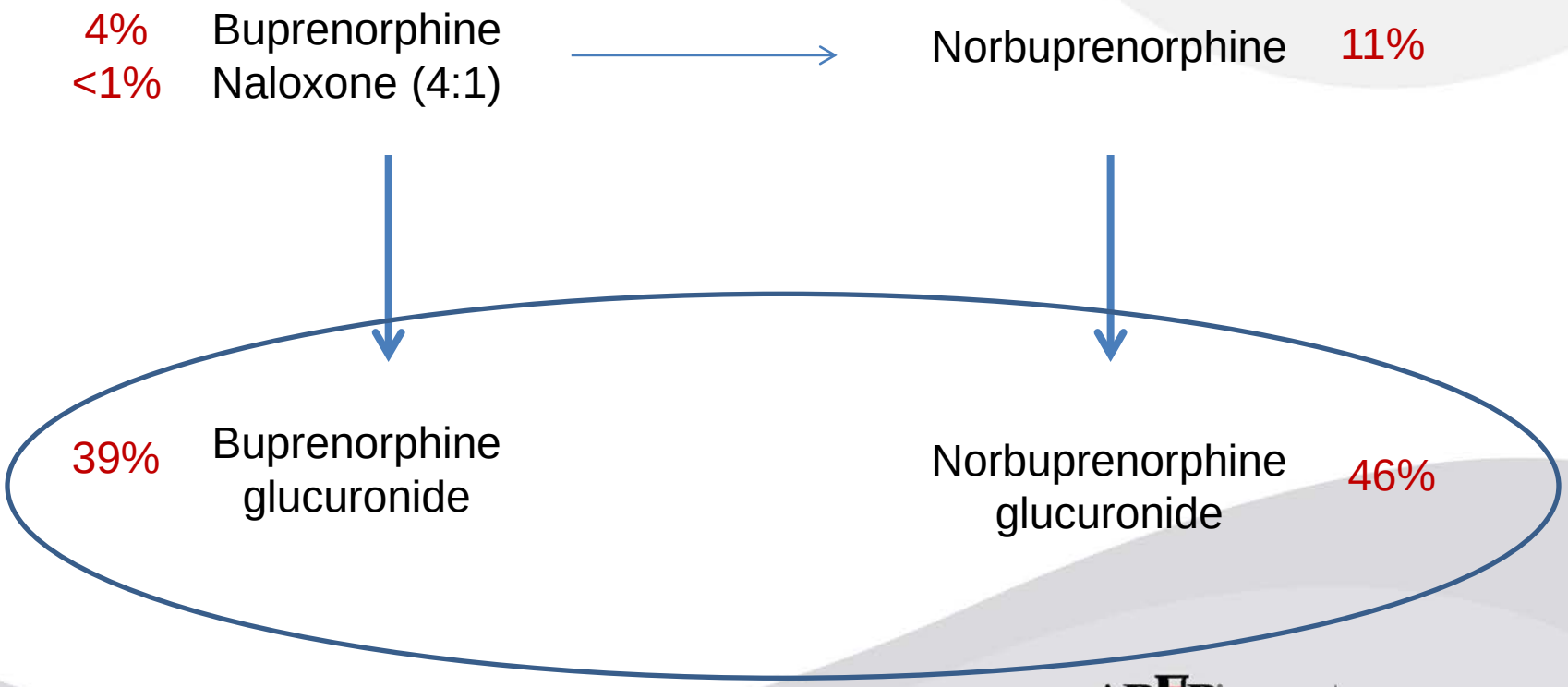
Will these tests detect urine substitution or direct addition of drug to the urine?

Substitution may not be detected

Sample	Sample Check (%) Microgenics, CEDIA	Creatinine (mg/dL) Syva (Dade), EMIT
Human urine	**80-100**	**> 5 (DOT)**
Dog urine (n=7)	52 - 85	87 - 284
Horse urine (n=1)	92	104
Energy drinks (n=44)	72-103	0-63
Margarita mix (n=2)	73-74	71-76
Fruit juice (n=8)	39-81	0-62

VP Villena, *JAT* 34:39-44, 2010

Simplified metabolism of Suboxone® and proportions in urine



Results suggest drug was added

	BUP (ng/mL)	NORBUP (ng/mL)
1	**39,400**	24
2	**39,200**	36
3	**31,100**	20
4	**20,200**	23
5	**19,300**	11
6	**18,800**	31
7	**15,000**	7
8	**12,100**	14
9	**11,100**	12
10	**10,900**	7

NOTES:

Glucuronides were < 20 ng/mL

McMillin et al., *JAT* 36(2):81-7, 2012

Results suggest drug was added

	BUP (ng/mL)	NORBUP (ng/mL)	**Naloxone (ng/mL)**	BUP: Naloxone Ratio
1	**39,400**	24	**6,690**	5.9
2	**39,200**	36	**9,560**	4.1
3	**31,100**	20	**8,500**	3.7
4	**20,200**	23	**5,160**	3.9
5	**19,300**	11	**4,470**	4.3
6	**18,800**	31	**4,430**	4.2
7	**15,000**	7	**2,300**	6.5
8	**12,100**	14	**3,110**	3.9
9	**11,100**	12	**2,920**	3.8
10	**10,900**	7	**3,010**	3.6

NOTES:

Expected ratio of BUP:Naloxone for Suboxone® = 4

Average ratio of BUP:Naloxone for these patients: 4.4

McMillin et al., *JAT* 36(2):81-7, 2012

Why use blood for drug testing?

- Urine substitution is suspected
- Dialysis patients
- Evaluate pharmacokinetics
  - Unpredictable drug absorption (e.g. bariatric surgery, Crohn's disease)
  - Suspicious drug delivery/bioavailability
  - Polypharmacy (drug-drug interactions)
  - Altered metabolic status
  - TDM

Conclusions

- Clinical laboratories are in an excellent position to actively participate, and/or consult, regarding the drug testing needs of chronic pain management patients

- Utilization of testing should be based on the clinical needs and test performance characteristics, rather than traditional reflex testing approaches

ARUP® LABORATORIES