National Laboratory Certification Program
DRUG TESTING MATTERS

2025

Opioid Hydrolysis Issues in Urine Drug Testing

Hydrolysis is essential to quantify opioids in urine correctly, but the efficiency varies between analytes and samples. Ensuring sufficient hydrolysis can be challenging, and insufficient hydrolysis sometimes causes erroneous results.

Opioids are a class of drugs that includes naturally occurring alkaloids from the opium plant, semi-synthetic derivatives of these alkaloids, and synthetic drugs that act on the same targets in the brain. There are several naturally occurring opium alkaloids, and they fall into two major classes: phenanthrenes and benzylisoquinolines (**Exhibit 1**). The primary phenanthrenes are morphine, codeine, and thebaine whereas the common benzylisoquinolines are papaverine and noscapine.[1, 2] Semi-synthetic opioids such as heroin and the pain relievers oxycodone, hydrocodone, oxymorphone, and hydromorphone are made in pharmaceutical manufacturing facilities by chemically processing natural opioids. Synthetic opioids such as fentanyl are manufactured without natural ingredients.[3]

The term "opioids," often used interchangeably with the term "opiates," is defined simply as compounds that have agonist or partial agonist activity at the opioid receptors and may or may not have structural similarity to the principal opium alkaloids. The term "opiates" is defined as compounds extracted or refined from the poppy plant. All opiates (e.g., codeine and morphine) can also be classified as opioids, but not all opioids (e.g., fentanyl, methadone, and meperidine) are classified as opiates.[1, 2]

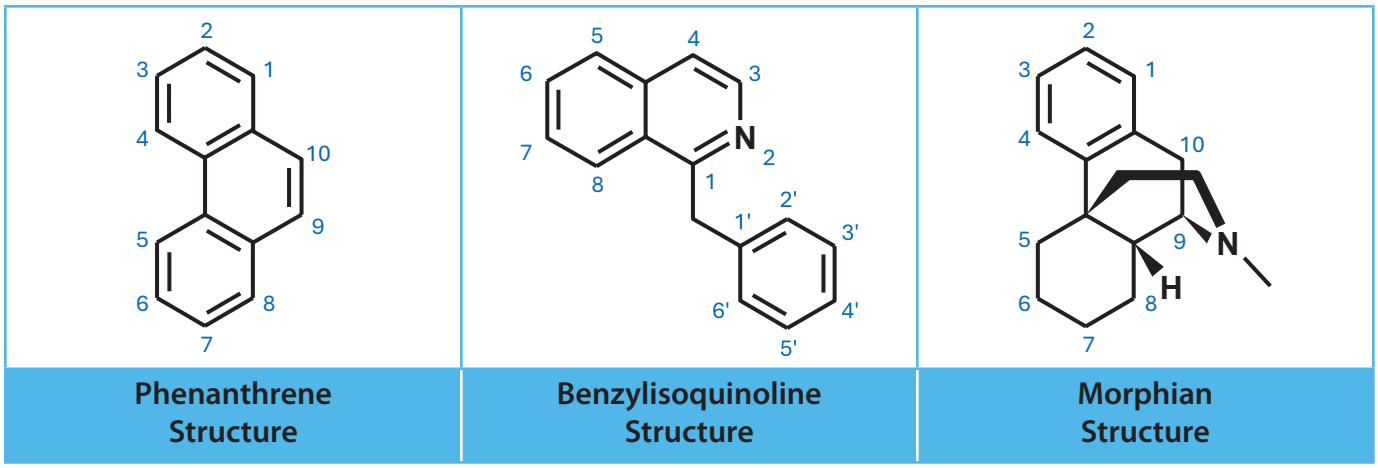

Exhibit 1. *Opiate framework structures*

Some opioids have a morphinan structure (**Exhibit 1**) at the core, and most have a free hydroxyl group (i.e., -OH) that forms the O-glycosidic linkage with glucuronic acid during phase II metabolism. They exist as bound (i.e., glucuronide conjugate) and unbound (i.e., "free") drugs in urine. In urine drug testing, opioids are commonly subjected to a deconjugation process (hydrolysis) to decouple or cleave conjugated opioids (e.g., codeine glucuronide and morphine-glucuronide) as part of sample preparation for confirmatory analysis. This article focuses on hydrolysis issues concerning glucuronides of the opioids in the U.S. Department of Health and Human Services (HHS) Authorized Drug Testing Panel (i.e., codeine, morphine, hydromorphone, and oxymorphone).

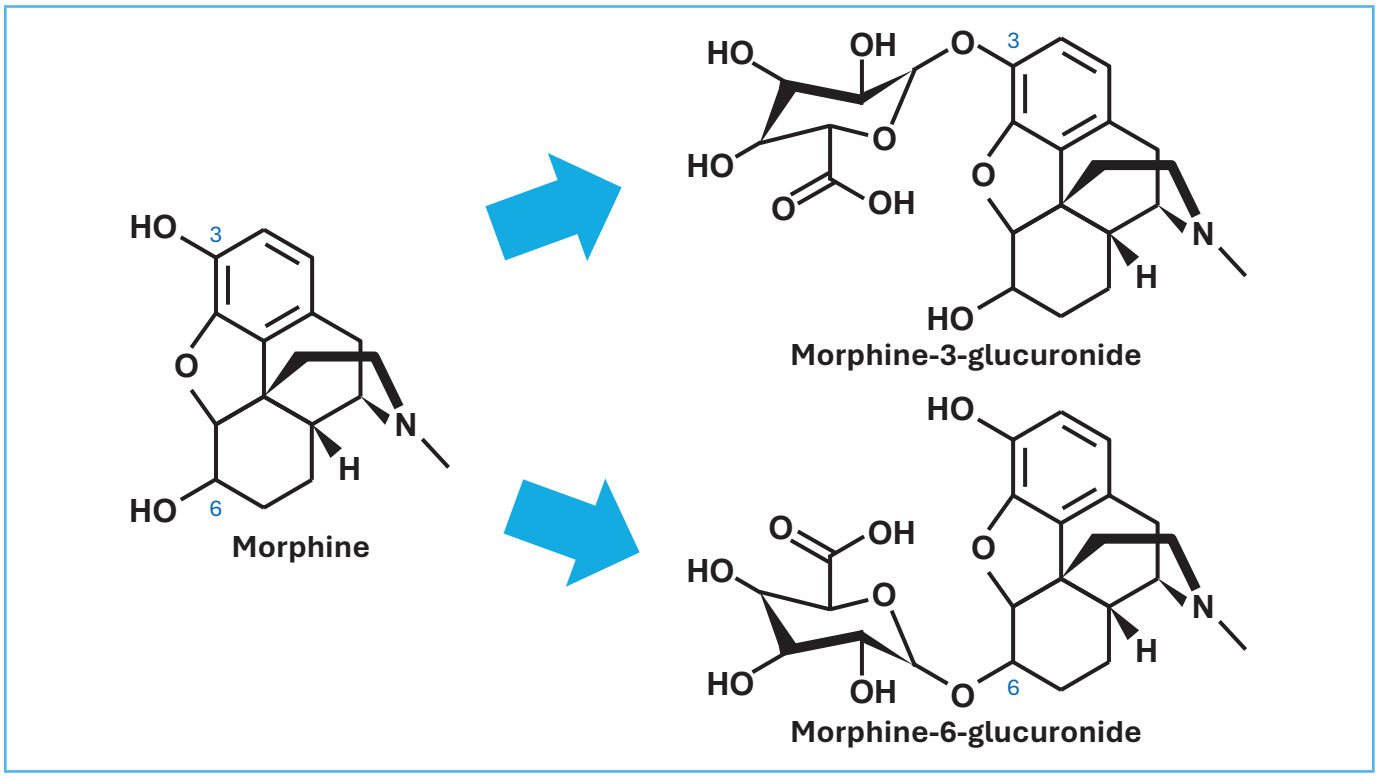

Exhibit 2. *Morphine conjugation*

As shown in **Exhibit 2**, morphine is a phenanthrene derivative consisting of a benzene ring with a phenolic hydroxyl group at position 3 and a hydroxyl group at position 6, with a methyl group on the nitrogen atom. Morphine undergoes extensive phase II conjugation via glucuronidation (i.e., conjugation with glucuronic acid) and sulfation. The glucuronidation process occurs at the C3-OH and C6-OH positions to form two main metabolites: morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G). Approximately 75% of a dose of morphine is excreted as the M-3-G conjugate. The unconjugated morphine (i.e., "free") accounts for approximately 10% of the dose.[4, 5] Trace amounts of M-6-G (potent analgesic metabolite of morphine), morphine-3-ethereal sulfate, and morphine-3,6-diglucuronide are also formed during the biotransformation of morphine.[4, 6]

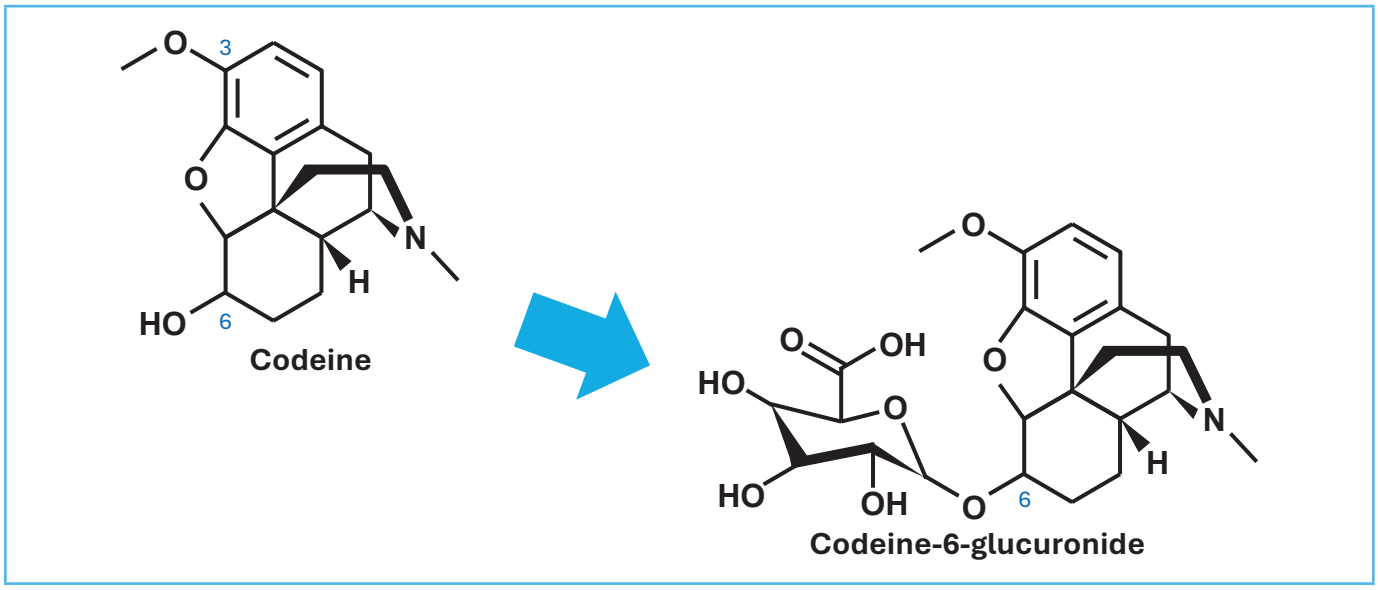

Exhibit 3. *Codeine conjugation*

As shown in **Exhibit 3**, codeine is a phenanthrene derivative consisting of a benzene ring with a phenolic O-methylated group (-O-CH3) at position 3 and an alcohol hydroxyl group (-OH) at position 6, with a methyl group (-CH3) on the nitrogen atom.[2, 7] Codeine undergoes extensive phase II conjugation with glucuronic acid via an alcohol hydroxyl group (i.e., -OH) at position 6 to form codeine-6-glucuronide. Approximately 10%–15% of codeine is N-demethylated to form norcodeine (a metabolite with no analgesic properties) by cytochrome P450 enzyme 3A4. A small proportion (5%–10%) of codeine is O-demethylated to form morphine by the cytochrome enzyme P450 isoform 2D6 (CYP2D6). Codeine is a prodrug (i.e., a pharmacologically inactive drug that is metabolized after intake into a pharmacologically active drug), and its analgesic properties are primarily dependent on its biotransformation into morphine.[8]

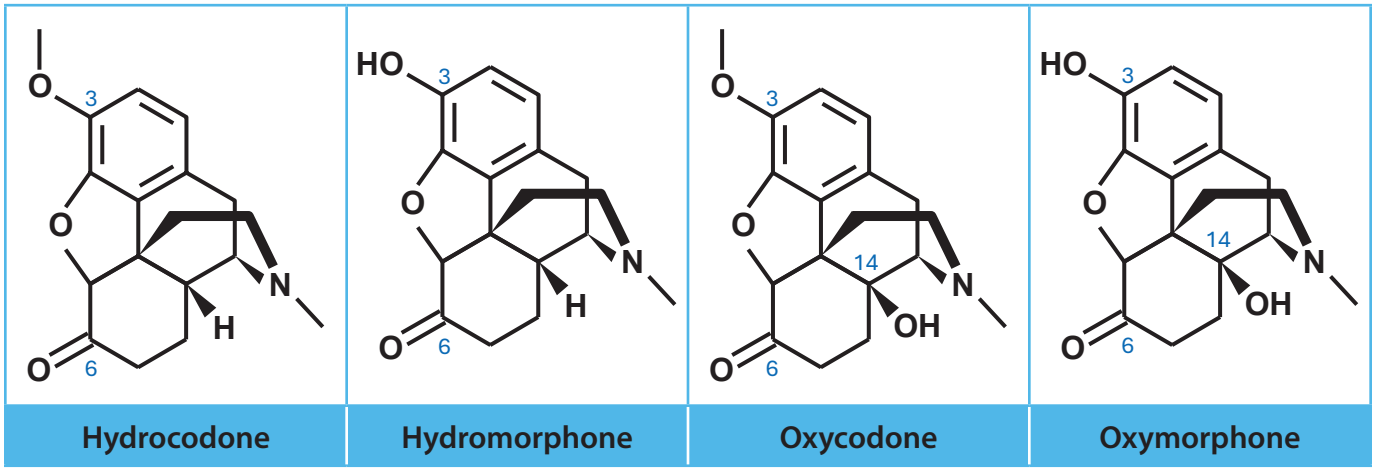

Exhibit 4. *Semi-synthetic opioids*

Exhibit 4 shows the structures of the four semi-synthetic opioids authorized for testing in federally regulated workplace drug testing programs.

Hydromorphone is a phenanthrene derivative consisting of a benzene ring with a phenolic hydroxyl group at position 3 and a ketone group at position 6, with a methyl group on the nitrogen atom. Hydromorphone undergoes hepatic biotransformation via conjugation with glucuronic acid to produce its primary metabolite, hydromorphone-3-glucuronide.[5]

Oxymorphone is a phenanthrene derivative consisting of a benzene ring with a phenolic hydroxyl group at position 3, a ketone group at position 6, and a hydroxyl group at position 14, with a methyl group on the nitrogen atom. Oxymorphone undergoes hepatic biotransformation via conjugation with glucuronic acid to produce its primary metabolite, oxymorphone-3-glucuronide.[5]

Hydrocodone is a phenanthrene derivative consisting of a benzene ring with a phenolic O-methylated group at position 3 and a ketone group at position 6, with a methyl group on the nitrogen atom.

Oxycodone is a phenanthrene derivative consisting of a benzene ring with a phenolic O-methylated group at position 3, a ketone group at position 6, and a hydroxyl group at position 14, with a methyl group on the nitrogen atom.

Because hydrocodone and oxycodone do not have a free hydroxyl group, conjugation to form corresponding glucuronide or sulfate appears to be minimal.[9] In one study, the recovery for urine oxycodone as the parent drug was 99% without hydrolysis, indicating that no hydrolysis is required for the parent drug.[9] Essentially the same conclusion was reached in a separate investigation by Lalovic et al.[10]

Opioid hydrolysis in the National Laboratory Certification Program (NLCP)

In urine drug testing, hydrolysis is used to decouple or cleave conjugated glucuronic acid from opioids before the free drug is extracted from urine and quantified using gas chromatography mass spectrometry (GC-MS) or liquid chromatography tandem mass spectrometry (LC-MS/MS) techniques.[11] Both acid hydrolysis (e.g., using hydrochloric acid) and enzyme hydrolysis (e.g., using β-glucuronidase or β-glucuronidase in combination with sulfatase) have been reported as viable methods, with the

former often reported as a more effective process for recovering codeine-6-glucuronide and morphine-6-glucuronide.[12] However, different authors have reported that acid-catalyzed opioid hydrolysis may result in significant loss of analytes.

For effective recovery of opioids from urine, most laboratories currently certified by HHS perform opioid hydrolysis using β-glucuronidase enzymes from different suppliers (e.g., Kura BioTech, IMCS, Sigma, and ChemSci Technologies) or from the same biological source through a different supplier. However, two current HHS-certified laboratories use acid hydrolysis whereas a third laboratory uses acid hydrolysis for their codeine/morphine and oxycodone/oxymorphone assays and enzyme hydrolysis for their hydrocodone/hydromorphone assay. The *HHS Mandatory Guidelines and the February 2024 NLCP Manual for Urine Laboratories*, rev. 0425 [11, 13] require laboratories to perform a hydrolysis study for opioid confirmatory drug tests to document acceptable hydrolysis before implementation on regulated specimens. For laboratories using enzyme hydrolysis, each new enzyme lot must be checked against the previous lot to demonstrate acceptable hydrolysis before being placed into service. In validation studies for codeine and morphine, laboratories must document acceptable hydrolysis (i.e., at least 80% recovery) by accurately quantifying samples with at least 15,000 ng/mL each of codeine-6-glucuronide and a morphine glucuronide (i.e., corresponding to at least 15,000 ng/mL of each free drug). In validation studies for oxymorphone and hydromorphone, laboratories must accurately quantify samples with at least 1,000 ng/mL each of oxymorphone-3-glucuronide and hydromorphone-3-glucuronide (i.e., corresponding to at least 1,000 ng/mL of each free drug). Laboratories must document acceptable performance at the same concentrations in re-verification studies, unless the laboratory's hydrolysis controls included in each batch are at or above 15,000 ng/mL (codeine/morphine) or 1,000 ng/mL (hydromorphone/oxymorphone).[11]

Factors Affecting Efficiency of Enzyme Hydrolysis

Lee et al.[14] have shown that enzyme hydrolysis performance in clinical urine specimens is highly dependent on the following:

- The nature or composition of the sample matrix. Differences in β-glucuronidase enzymes' tolerance to specific biological and chemical elements (i.e., endogenous non-target substrates) present in samples that can interfere with drug target hydrolysis, either inhibiting activity or inactivating the enzyme. A robust and active enzyme is expected to exhibit consistent performance regardless of the heterogeneity of the urine samples.
- The pH of the reaction buffer.
- Adequate urine pH adjustment for optimum hydrolysis using buffers (volume ratio of buffer to urine). For some analytes, a pH change of 0.5 units can significantly alter hydrolysis efficiency. A pH change can sometimes increase efficiency for some analytes and decrease it for others.
- Enzyme-unique substrate biases. An ideal enzyme should have uniform activities across multiple substrates and a broad pH range.
- The enzyme temperature and catalytic activity for a glucuronidated drug, with optimal conditions necessary for efficient hydrolysis.
- Incubation time and temperature.
- The amount of enzyme used during hydrolysis (i.e., enzyme load).

In their findings, Lee et al. indicated that successful hydrolysis depends upon a complex interaction between enzymes, substrates (i.e. glucuronidated drug), and matrix to achieve quantitative yield of target analytes. Purified β-glucuronidases were compared to show enzyme-dependent biases on a panel of common drug targets (e.g., opioids, benzodiazepines, illicit substances, and tricyclics). They also tested patient urine samples with a range of pHs to show the interdependence of pH on both enzyme and substrate. In evaluating new β-glucuronidases that are designed to perform hydrolysis at room temperature, the authors indicated that unsuccessful pH adjustment after buffer addition to clinical samples is likely to occur in some samples that exhibit abnormally high or low pH levels. Such samples would require larger amounts of buffer to achieve optimum pH for hydrolysis, and the enzyme performance would be impacted differently for each substrate. Some urine patient samples with acidic pH values needed lesser amounts of buffer (mostly 1:1 buffer:urine ratio) to adjust pH, while samples with basic pH values required more buffer (mostly 3:1 buffer:urine ratio) to adjust the pH. They indicated that such challenges in urine pH adjustment can further compromise enzyme hydrolysis efficiency, potentially leading to low recovery and inaccurate quantification. Additionally, the authors demonstrated that β-glucuronidases have different pH and substrate profiles. Therefore it is insufficient to rely on a single substrate in synthetic matrix or a single pH as a benchmark to compare enzyme performance.

In a separate study conducted by Wang et al.,[9] acid hydrolysis liberated greater than 90% of morphine and hydromorphone from their glucuronide standards, and enzyme hydrolysis had lower and variable efficiency depending on the opiate type and the enzyme source. In patient specimens analyzed by Wang et al., much higher concentrations of free codeine, morphine, hydromorphone, and oxymorphone were obtained with acid hydrolysis than with various enzyme methods. The authors concluded that incomplete hydrolysis using β-glucuronidase could lead to false-negative results for some opioids.

Other authors (e.g., Sitasuwan et al.[12]) raised concerns with acid-catalyzed hydrolysis of opioids. In their study of acid hydrolysis conducted at 95°C for 90 minutes, they reported incremental loss of both oxycodone and hydrocodone and increased concentrations of demethylated analytes (i.e., oxymorphone and hydromorphone, respectively) over time. They suggested that other degradation processes were present because the increase in oxymorphone and hydromorphone was not proportional to the loss of their original compounds. For samples incubated with concentrated acid at a lower temperature of 55°C, they reported no conversion of oxycodone to oxymorphone, indicating that the higher temperature is necessary for the degradation of the opioid. However, lowering the temperature to 55°C reduced the hydrolysis efficiency of hydromorphone and oxymorphone glucuronides, nullifying the advantage in processing speeds compared to enzymatic hydrolysis. Conversion was not observed when using enzymatic hydrolysis, and the authors concluded that enzymatic hydrolysis using the purified, genetically engineered β-glucuronidase (IMCSzyme) addresses many of the concerns associated with acid hydrolysis and demonstrates accurate quantification and high recoveries for hydromorphone, oxymorphone, hydrocodone, and oxycodone.

NLCP performance testing

The NLCP performance testing (PT) program is designed to challenge various aspects of laboratories' test procedures (i.e., initial testing, confirmatory testing, quantification, and reporting). To assess laboratories' opioid hydrolysis procedures each year, the NLCP produces samples containing different combinations of free and conjugated morphine, hydromorphone, and oxymorphone and sample(s) with codeine glucuronide from pooled donor specimens that had high codeine concentrations. Some laboratories have to dilute the highly concentrated samples to obtain a result within the linear range of their assay. Other laboratories have an upper limit of linearity (ULOL) of 20,000 ng/mL and do not perform a dilution. There were not many PT errors on these samples in 2023–2024:

- Occasion 145. Sample with M-3-G at 15,000 ng/mL: one laboratory had a 20% error (high).
- Occasion 145. Sample with 1,000 ng/mL OXYM-glucuronide, 1,000 ng/mL HYM-glucuronide, and 700 ng/mL HYM: no errors.
- Occasion 146. Codeine pooled donor sample; codeine mean was 10,079 ng/mL: one laboratory had a 20% error (high), and another laboratory had a 20% error (low).
- Occasion 146. Sample with 1,000 ng/mL OXYM-glucuronide and 10,000 ng/mL HYM-glucuronide: no errors.
- Occasion 147. Sample with M-3-G at 15,000 ng/mL: no errors.
- Occasion 148. Codeine pooled donor sample; codeine mean was 10,266 ng/mL: one laboratory had a major error for codeine (*reagents were close to expiration, laboratory shortened expiration period*).
- Occasion 148. Sample with M-3-G at 1,000 ng/mL and free morphine at 2,000 ng/mL: one laboratory had a 20% error (high).
- Occasion 149. Sample with M-3-G 15,000 ng/mL: one laboratory had a 20% error (low).
- Occasion 149. Sample with 1,000 ng/mL OXYM-glucuronide, 1,000 ng/mL HYM-glucuronide, and 350 ng/mL HYM: one laboratory had a 20% error (high).
- Occasion 150. Codeine pooled donor sample; codeine mean was 12,096 ng/mL: one laboratory had a 20% error (low).
- Occasion 150. Sample with 1,000 ng/mL OXYM-glucuronide and 10,000 ng/mL HYM-glucuronide: no errors.
- Occasion 151. Sample with M-3-G at 15,000 ng/mL: no errors.
- Occasion 152. Codeine pooled donor sample, codeine mean was 12,330 ng/mL: no errors.
- Occasion 152. Sample with M-3-G at 1,000 ng/mL, free morphine at 2,500 ng/mL: no errors.

Opioid Retest Inconsistencies from HHS-certified laboratories

Laboratories notify the NLCP when results for primary (A) and split (B) bottles of a specimen are inconsistent. Four examples are presented here.

Case #1 (Codeine Inconsistencies)					
	Lab A Bottle A	**Lab A Re-analysis of Bottle A**	**Lab B Bottle B**	**Lab C Aliquot of Bottle A**	**Lab C Aliquot of Bottle B**
Codeine LC-MS/MS (A, C) GC-MS (B)	5,770 ng/mL	6,991 ng/mL (**×2 dilution**) 11,138 ng/mL (**×5 dilution**)	13,088 ng/mL 13,117 ng/mL	13,322 ng/mL	14,234 ng/mL
Morphine	873 ng/mL	836 ng/mL 915 ng/mL	775 ng/mL 796 ng/mL	737 ng/mL	805 ng/mL

- Lab A used recombinant β-glucuronidase enzyme from IMCS.
- Lab B used β-glucuronidase (Kura Biotec) that is 100,000 units/mL from red abalone.
- Lab C used enzyme BGTurbo Glycerol Free, High-Efficiency Recombinant β-Glucuronidase (Kura Biotec).
- Lab C's codeine results for the aliquots of the A and B bottles were consistent with Lab B's codeine results for Bottle B, and Lab A's re-analysis codeine result performed at **a ×5 dilution**.
- Lab A re-analyzed the primary specimen undiluted (neat) using a different enzyme and hydrolysis condition. Lab A obtained a codeine result of **12,316 ng/mL** that was consistent with the results from Labs B and C. The morphine result of **922 ng/mL** was consistent with the laboratory's original result (873 ng/mL) for the primary specimen.
- The enzyme used by Lab A was not as effective at hydrolysis of this particular specimen.

Case #2 (Codeine Inconsistencies)			
Aliquot	**Lab A Bottle A**	**Lab B Bottle B**	**Lab C Aliquot of Bottle B**
1	6,620 ng/mL COD 2,830 ng/mL MOR	35,722 ng/mL COD 3,405 ng/mL MOR (**×10 dilution**)	25,639 ng/mL COD 3,071 ng/mL MOR (**×2 dilution**) Acid hydrolysis
2	5,721 ng/mL COD 2,511 ng/mL MOR	>ULOL COD 3,161 ng/mL MOR (**No dilution**)	25,538 ng/mL COD 3,093 ng/mL MOR (**×10 dilution**) Acid hydrolysis
3	NA	36,116 ng/mL COD 3,802 ng/mL MOR (**×10 dilution**)	2,558 ng/mL COD 131 ng/mL MOR (**×2 dilution**) No hydrolysis
4	NA	34,858 ng/mL COD 3,583 ng/mL MOR (**×5 dilution**)	2,551 ng/mL COD 133 ng/mL MOR (**×10 dilution**) No hydrolysis

- Both the A and B labs performed enzyme hydrolysis using β-glucuronidase from the same biological source (abalone) but from different suppliers.
- Lab C used acid hydrolysis for additional testing. Lab C also performed additional testing with no hydrolysis.
- Lab C confirmed Lab B's codeine results for the B specimen using acid hydrolysis.
- The results from Case #2 indicate incomplete hydrolysis of codeine glucuronide when the specimen was analyzed at Lab A.
- Lab A changed their hydrolysis method to begin using β-glucuronidase enzyme from a different manufacturer and increased their incubation time. The revised assay yielded 99.9% recovery of codeine present as glucuronide.
- Lab A send an aliquot of Bottle A to Lab C; however, it was damaged and leaked during transit. There was insufficient volume in Bottle A for further testing.
- Labs A, B, and C analyzed the specimen using GC-MS instruments.

Case #3 (Codeine Inconsistencies)				
Aliquot	**Lab A Bottle A**	**Lab B Bottle B**	**Lab C Aliquot of Bottle A**	**Lab C Aliquot of Bottle B**
1	**8,009** ng/mL COD 910 ng/mL MOR	1,373 ng/mL COD 696 ng/mL MOR (**No dilution**)	1,021 ng/mL COD 234 ng/mL MOR (**No dilution**)	996 ng/mL COD 241 ng/mL MOR (**No dilution**)
2	**8,018** ng/mL COD 877 ng/mL MOR	1,231 ng/mL COD 662 ng/mL MOR (**No dilution**)	**9,284** ng/mL COD **1,093** ng/mL MOR (**×5 dilution**)	**8,622** ng/mL COD **1,026** ng/mL MOR (**×5 dilution**)
3	NA	**8,089** ng/mL COD 908 ng/mL MOR (**×5 dilution**)	NA	NA

- Lab A performed enzyme hydrolysis using BGTurbo High Efficiency Recombinant Beta-Glucuronidase by Kura Biotech.
- Lab B performed enzyme hydrolysis using β-glucuronidase from "Red abalone" (Kura Biotech).
- Lab C used β-glucuronidase enzyme from IMCS.
- Labs A and B analyzed the specimen using LC-MS/MS instruments.
- Lab C analyzed the aliquots of Bottles A and B using a GC-MS/MS instrument.
- Lab B's codeine results when the B specimen was analyzed undiluted indicate incomplete hydrolysis of codeine present as glucuronide.
- Lab C's codeine results indicate incomplete hydrolysis of codeine and morphine glucuronides when the specimen (i.e., aliquots of Bottles A and B) was analyzed undiluted at Lab C.
- The re-analysis of the specimen at a ×5 dilution at Labs B and C appears to yield complete hydrolysis of codeine and morphine present as glucuronides indicating possible matrix interference when the specimen was not diluted.
- pH meter results for this specimen were ≥9.0.

Case #4 (Hydromorphone and Oxymorphone Inconsistencies)		
Aliquot	**Lab A Bottle A**	**Lab B Bottle B**
1	2,195 ng/mL HYM 3,433 ng/mL OXYM **(No dilution)**	**5,730** ng/mL HYM **16,371** ng/mL OXYM (mass ratio not acceptable) (**No dilution**)
2	**8517** ng/mL HYM **18,185** ng/mL OXYM **(×10 dilution)**	**18,291 ng/mL OXYM** (**×21 dilution**)
3	6,768 ng/mL HYM >10,000 ng/mL OXYM (No dilution) New enzyme	

- Lab A revised their hydrolysis procedure, including the enzyme used.

Conclusion

Pre-analytical hydrolysis to convert conjugated drugs/metabolites into the unbound (free) form is required to detect and accurately quantitate opioids that are highly metabolized by glucuronidation and sulfation.[15] The efficiency of various hydrolysis protocols varies between different drugs/metabolites, necessitating rigorous method validation. This article shows a few examples where the hydrolysis has been insufficient, yielding low results discovered as retest inconsistencies upon testing by another laboratory.

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